Therapy of Skin Diseases
Thomas Krieg
David R. Bickers
Yoshiki Miyachi (Eds.)

Therapy of Skin Diseases
A Worldwide Perspective on Therapeutic Approaches and Their Molecular Basis
Treatment of skin diseases has changed remarkably during the last decade. This is largely the result of a better understanding of the molecular and cellular basis of many skin diseases. Thus, novel targets have been identified and specific drugs developed which directly interfere with or alter the disease processes. This change is readily apparent when considering the novel agents available for psoriasis and atopic dermatitis, and also for viral and other infectious skin diseases. Interestingly, many of these new agents are administered systemically either orally or by subcutaneous injection. And yet, as with all forms of drug therapy, these highly efficacious agents can also be associated with severe side effects and drug-induced toxicity. Accordingly, the dermatologist must be aware of the medical status of the patient as well as all other medications that are being prescribed concomitantly. Careful monitoring of the risk:benefit ratio is always critical.

Simultaneously, with the rapid development of novel therapeutics, there has been a major evolution in the clinical practice of dermatology with considerable variations across different areas of the world. In European countries, the discipline is relatively broad, in some countries including allergy and phlebology, as well as dermatologic surgery and dermatologic oncology. In European countries, patients with skin disease are often treated as in-patients by dermatologists, whereas in the United States, this occurs only rarely and the patients are admitted to beds assigned to Internal Medicine and dermatologists consult on their management. Asian dermatology has been profoundly affected by both European and American dermatology and the selection of therapeutic agents often reflects those influences.

The result of these developments is that regional differences are commonplace in the treatment of skin diseases, some correlating with the dermatologic features of patients from diverse ethnic backgrounds, others relating to variations in the different health care systems and/or the medical education and the awareness of dermatologists regarding particular treatment options. In the age of Internet, novel therapies are instantly available and potentially applicable to patients globally.

This book was conceived to address these changes and it has two major aims. First, it summarizes novel therapeutic procedures that are based on understanding the pathophysiology of skin diseases. Second, it aims to bring together in one place the variability of treatment modalities employed in the practice of dermatology around the world in Asia, Europe, and the USA. Every effort has been made to assure that all chapters indicate global variations either in the occurrence or the expression of skin
diseases and their treatment. All manuscripts have been reviewed carefully by experts familiar with the practice of dermatology in Asia, Europe, and the USA. It is our hope that this book will prove to be a valuable reference tool for dermatologists everywhere.

Köln, Germany
New York, USA
Kyoto, Japan

Thomas Krieg
David R. Bickers
Yoshiki Miyachi
We owe special acknowledgement to the cooperation of
Walter Burgdorf, MD
Traubinger Strasse 54A, 82327 Tutzing, wburgdorf@gmx.de
and
Mayumi Fujita, MD, PhD
Associate Professor,
Department of Dermatology, University of Colorado Denver, SOM, Mail Stop 8127,
RC-1 South 4th fl., 12801 E 17th Avenue, Aurora, CO 80045, USA,
mayumi.fujita@ucdenver.edu
# Contents

**Part I Introduction** ................................................................. 1  

1.1 **Biology of the Skin** ....................................................... 3  
Beate Eckes, Thomas Krieg, and Carien M. Niessen  

1.2 **Immune Mechanisms** .................................................... 15  
Thomas Schwarz and Stefan Beissert  

1.3 **General Pharmacology** ................................................... 21  
David R. Bickers  

1.4 **Immunomodulation in Dermatology** ................................. 29  
Rebecca G. Pomerantz, Thomas S. Kupper, and Abrar A. Qureshi  

1.5 **Basic Principles of Genetics and Gene Therapy** .................. 39  
Liv Kraemer and Angela M. Christiano  

1.6 **Percutaneous Absorption and Principles of Corneotherapy/Skin Care** ........................................ 57  
Hachiro Tagami  

1.7 **Principles of Systemic Therapy** ...................................... 63  
Lindy P. Fox  

1.8 **Retinoid Pharmacology** .................................................. 77  
Jens M. Baron  

1.9 **Ultraviolet (UV) A and (UV) B Phototherapy** ...................... 87  
Akimichi Morita  

1.10 **Laser Therapy** .............................................................. 93  
David J. Goldberg  

1.11 **Photodynamic Therapy** .................................................. 105  
Yoshiki Tokura and Shin-ichi Moriwaki  

1.12 **Dermatologic Surgery** ................................................... 113  
Murad Alam
### 1.13 Neurophysiology of Itch
Akihiko Ikoma

### Part II Infectious Diseases

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>Bacterial and Mycobacterial Infections</td>
<td>Nicole French and Robert L. Modlin</td>
</tr>
<tr>
<td>2.2</td>
<td>Fungal Infection</td>
<td>Takashi Mochizuki</td>
</tr>
<tr>
<td>2.3</td>
<td>Viral Infections</td>
<td>Annabelle Lozano, Anita Arora, Natalia Mendoza, Vandana Madkan, and Stephen K. Tyring</td>
</tr>
<tr>
<td>2.4</td>
<td>Sexually Transmitted Diseases (STDs)</td>
<td>Anja Potthoff, Heinrich Rasokat, and Norbert H. Brockmeyer</td>
</tr>
<tr>
<td>2.5</td>
<td>Human Immunodeficiency Virus (HIV)</td>
<td>Anja Potthoff, Heinrich Rasokat, and Norbert H. Brockmeyer</td>
</tr>
<tr>
<td>2.6</td>
<td>Ectoparasitic and Protozoan Diseases</td>
<td>Dirk M. Elston</td>
</tr>
</tbody>
</table>

### Part III Papulosquamous Dermatoses

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
<td>Psoriasis</td>
<td>Hajime Iizuka</td>
</tr>
<tr>
<td>3.2</td>
<td>Parapsoriasis and Related Disorders</td>
<td>Peter C. M. van de Kerkhof</td>
</tr>
<tr>
<td>3.3</td>
<td>Lichen Planus</td>
<td>Tetsuo Shiohara, Yoshiko Mizukawa, and Yoko Kano</td>
</tr>
</tbody>
</table>

### Part IV Atopic Dermatitis and Related Diseases

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1</td>
<td>Atopic Dermatitis</td>
<td>Andreas Wollenberg and Thomas Bieber</td>
</tr>
<tr>
<td>4.2</td>
<td>Pruritus</td>
<td>Sonja Ständer and Thomas A. Luger</td>
</tr>
<tr>
<td>4.3</td>
<td>Urticaria</td>
<td>Michihiro Hide</td>
</tr>
<tr>
<td>4.4</td>
<td>Mastocytosis</td>
<td>Naotomo Kambe, Akane Tanaka, and Yoshiki Miyachi</td>
</tr>
</tbody>
</table>
Part V  Allergic Reactions and Hypersensitive Diseases .......................... 273

5.1  Allergic Contact Dermatitis  .................................................. 275
Cecilia Svedman and Magnus Bruze

5.2  Photosensitivity Diseases .......................................................... 285
Taskeshi Horio

5.3  Drug Reactions ................................................................. 297
Hans F. Merk and Daniela Höller Obrigkeit

5.4  Hypersensitivity Syndrome Reaction ........................................ 321
Sandra R. Knowles and Neil H. Shear

5.5  Eosinophilic Dermatoses ...................................................... 327
Ichiro Katayama and Hiroyuki Murota

5.6  Neutrophilic Dermatoses ....................................................... 337
Tadashi Terui

5.7  Skin Manifestations in Rheumatologic Disorders ....................... 349
Manabu Fujimoto and Kazuhiko Takehara

Part VI  Acne and Rosacea ............................................................. 357

6.1  Acne and Its Variants .......................................................... 359
Christos C. Zouboulis and Mohamed Badawy Abdel-Naser

6.2  Rosacea and Related Diseases ................................................ 375
Mohamed Badawy Abdel-Naser and Christos C. Zouboulis

Part VII  Autoimmune Diseases ....................................................... 387

7.1  Acquired Bullous Disease ..................................................... 389
Akiko Tanikawa and Masayuki Amagai

7.2  Connective Tissue Diseases ................................................... 407
Minoru Hasegawa and Shinichi Sato

7.3  Cutaneous Vasculitis ........................................................... 427
Nicolas Hunzelmann

7.4  Graft-Versus-Host Disease .................................................... 433
Robert Knobler, Michal Kouba, and David Pohlreich

7.5  Vitiligo ................................................................. 443
Philippe Bahadoran and Jean-Paul Ortonne
7.6 Therapy of Noninfectious Granulomatous Diseases ........................... 459
Franco Rongioletti and Alfredo Rebora

Part VIII Metabolic Diseases .......................................................... 467

8.1 The Porphyrias ................................................................. 469
Jorge Frank

8.2 Deposition Diseases .......................................................... 487
Takahiro Hamada

Part IX Cosmetic Dermatology ...................................................... 497

9.1 Hair Diseases (Alopecia Areata and Androgenetic Alopecia) ........ 499
Satoshi Itami and Shigeki Inui

9.2 Nail Diseases ................................................................. 509
Maurice J. Dahdah and Richard K. Scher

9.3 Hyperhidrosis ................................................................. 517
Robyn D. Siperstein and Robert A. Schwartz

9.4 Disorders of Pigmentation .................................................. 525
Yoko Funasaka

9.5 Cosmetic Surgery ............................................................ 539
Murad Alam

Part X Inherited Diseases ............................................................... 547

10.1 Inherited Bullous Diseases ............................................... 549
Leena Bruckner-Tuderman and Cristina Has

10.2 Inherited Keratinocyte Diseases
(Ichthyosis and Related Disorders) ........................................... 561
Akemi Ishida-Yamamoto

10.3 Immunodeficiency Disorders ........................................... 575
Giuseppe Micali, Dennis P. West, and Amy S. Paller

10.4 Disorders of DNA Repair ................................................ 589
Shinichi Moriwaki and Kenneth H. Kraemer

Part XI Benign and Malignant Tumors ........................................... 597

11.1 Nonmelanoma Skin Cancer ............................................. 599
Alexander G. Marneros and David R. Bickers

11.2 Malignant Melanoma ........................................................ 621
Toshiaki Saida
11.3 Treatment of Cutaneous Lymphomas .......................... 633
Chalid Assaf and Wolfram Sterry

11.4 Vascular Malformations ................................. 643
Maria C. Garzon and Philip M. Meyers

11.5 Rare Malignancies of the Skin ......................... 659
Bernhard Zelger and Oliver Bechter

Part XII Miscellaneous Disorders ......................... 675

12.1 Diseases of Pregnancy and Their Management ........... 677
George Kroumpouzos and Lisa M. Cohen

12.2 Pediatric Dermatology .................................. 693
Alain Taïeb, Franck Boralevi, and Christine Labrèze

12.3 Aging and Photoaging of the Skin .................. 705
Laure Rittié, Gary J. Fisher, and John J. Voorhees

12.4 Occupational Dermatoses ............................. 717
S. Mark Wilkinson and Pieter-Jan Coenraads

12.5 Wound Healing ........................................ 735
Sabine A. Eming

Subject Index ............................................. 753
Mohamed Badawy Abdel-Naser, MD  Departments of Dermatology, Venereology, Allergology and Immunology, Dessau Medical Center, Auenweg 38, 06847 Dessau, Germany, abdelnasermb@yahoo.com

Murad Alam, MD  Northwestern University Dermatology, Clinical Trials Unit, 676 N St Clair, Suite 1600, Chicago, IL 60611, USA m-alam@northwestern.edu

Masayuki Amagai, MD, PhD  Department of Dermatology, Keio University, School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan amagai@sc.itc.keio.ac.jp

Anita Arora, MD  6655 Travis, Suite 120, Houston, TX 77030, USA aarora@ccstexas.com

Chalid Assaf, MD  Department of Dermatology, Helios Clinics Krefeld, Lutherplatz 40, 47805 Krefeld, Germany chalid.assaf@helios-kliniken.de

Philippe Bahadoran, MD  Service de Dermatologie, Hôpital l’Archet 2, CHU de Nice, Route St. Antoine Gnestière, 06202 Nice Cedex 3, France bahadoran@unice.fr

Jens Malte Baron, MD  Department of Dermatology and Allergology, University Hospital RWTH Aachen, Pauwelsstrasse 30, 52074 Aachen, Germany JensMalte.Baron@post.rwth-aachen.de

Oliver Bechter, MD  Department of Internal Medicine, Innsbruck Medical University, Anichstrasse 35, 6020 Innsbruck, Austria Oliver.Bechter@i-med.ac.at

Stefan Beissert, MD, PhD  Department of Dermatology, University of Münster, Von Esmarchstrasse 58, 48149 Münster, Germany beisser@uni-muenster.de

David R. Bickers, MD  New York Presbyterian Hospital, 161 Fort Washington Avenue, 12th floor, New York, NY 10032, USA drb25@columbia.edu

Thomas Bieber, MD, PhD  Department of Dermatology and Allergy, University of Bonn, Sigmund-Freud-Strasse 25, 53105 Bonn, Germany thomas.bieber@ukb.uni-bonn.de
Franck Boralevi, MD  Hôpital Pellegrin-Enfants, CHU de Bordeaux, Place Amélie Raba-Léon, 33076 Bordeaux Cedex, France
franck.boralevi@chu-bordeaux.fr

Norbert H. Brockmeyer, MD  Department of Dermatology and Allergology, Ruhr University Bochum, Gudrunstraße 56, 44791 Bochum, Germany
n.brockmeyer@derma.de

Leena Bruckner-Tuderman, MD  Department of Dermatology, University Medical Center Freiburg, Hauptstraße 7, 79104 Freiburg, Germany
bruckner-tuderman@uniklinik-freiburg.de

Magnus Bruze, MD  Department of Occupational and Environmental Dermatology, Malmö University Hospital, UMAS, Ing 73 (Entrance 45), S-205 02 Malmö, Sweden
magnus.bruze@med.lu.se

Angela M. Christiano, PhD  Department of Dermatology and Genetics and Development, Columbia University, College of Physicians and Surgeons, 630 West 168th Street VC15 204A, New York, NY 10032, USA
amc65@columbia.edu

Pieter-Jan Coenraads, MD  Occupational and Environmental Dermatology Unit, University Medical Center Groningen, Hanzeplein 1, 9700 RB Groningen, The Netherlands
j.coenraads@med.umcg.nl

Lisa M. Cohen, MD  Cohen Dermatopathology, 320 Needham Street, Suite 200, Newton, MA 02464, USA
lcohen@cohenderm.com

Maurice J. Dahdah, MD  Department of Dermatology, 161 Fort Washington Avenue, IP 12th floor, New York, NY 10032, USA
mmd2129@columbia.edu

Beate Eckes, PhD  Department of Dermatology, University of Cologne, Kerpener Straße 62, 50937 Cologne, Germany
beate.eckes@uni-koeln.de

Dirk M. Elston, MD  Department of Dermatology, Geisinger Medical Center, 100 North Academy Avenue, Danville, PA 17821, USA
Dmelston@geisinger.edu

Sabine A. Eming, MD  Department of Dermatology, University of Cologne, Kerpener Straße 62, 50937 Cologne, Germany
sabine.eming@uni-koeln.de

Gary J. Fisher, PhD  6447 Med Sci I, 1150 W Medical Center Drive, Ann Arbor, MI 48109-0609, USA
dianemch@umich.edu

Lindy P. Fox, MD  Department of Dermatology, University of California, San Francisco, 1701 Divisadero, Box 0316, San Francisco, CA 94143, USA
foxli@derm.ucsf.edu
Jorge Frank, MD, PhD  Maastricht University, Center for Molecular Dermatology, University Medical Center Maastricht, P. Debyelaan 25, 6202 AZ Maastricht, The Netherlands
jfna@sder.azm.nl

Nicole French, PhD  11963 Walnut Lane, Apt 5, Los Angeles, CA 90025, USA
nfrench@ucla.edu

Manabu Fujimoto, MD  Department of Dermatology, Kanazawa University, Graduate School of Medical Science, 13-1 Takaramachi, Kanazawa Ishikawa 920-8641, Japan
mfujimoto@derma.m.kanazawa-u.ac.jp

Yoko Funasaka, MD  Department of Clinical Molecular Medicine, Division of Dermatology, Kobe University School of Medicine, 7-5-1 Kusunoki-cho Chuo-ku, Kobe 650-0017, Japan
funasaka@med.kobe-u.ac.jp

Maria C. Garzon, MD  Department of Dermatology, Columbia University, College of Physicians and Surgeons, Herbert Irving Pavilion, 12th Floor, 161 Fort Washington Avenue, New York, NY 10032, USA
mcg2@columbia.edu

David J. Goldberg, MD  Clinical Professor of Dermatology, The Galleria, 115 E. 57th Street, Suite 10, New York, NY 10022, USA
drdavidgoldberg@drdavidgoldberg.com
Laser Research, Mount Sinai School of Medicine, New York, NY, USA

Takahiro Hamada, MD  Department of Dermatology, Kurume University School of Medicine, 67 Asahimachi, Kurume, Fukuoka 830-0011, Japan
hamataka@med.kurume-u.ac.jp

Cristina Has, MD  Department of Dermatology, University Medical Center Freiburg, Hauptstraße 7, 79104 Freiburg, Germany
cristina.has@uniklinik-freiburg.de

Minoru Hasegawa, MD, PhD  Department of Dermatology, Kanazawa University, Graduate School of Medical Science, 13-1, Takara-machi, Kanazawa, Ishikawa 920-8641, Japan
minoruha@derma.m.kanazawa-u.ac.jp

Michihiro Hide, MD, PhD  Department of Dermatology, Division of Molecular Medical Science, Graduate School of Biomedical Sciences Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan
mhidde@hiroshima-u.ac.jp

Taskeshi Horio, MD  Department of Dermatology, Kansai Medical University, Fumizono 10-15, Moriguchi, Osaka 570-8507, Japan
horio@takii.kmu.ac.jp

Nicolas Hunzelmann, MD  Department of Dermatology, University of Cologne, Kerpener Straße 62, 50937 Köln, Germany
Nico.Hunzelmann@uni-koeln.de
Hajime Iizuka, MD  Department of Dermatology, Asahikawa Medical College, 2-1-1-1 Higashi Midorigaoka, Asahikawa-Shi, Hokkaido 078-8510, Japan
derma@asahikawa-med.ac.jp

Akihiko Ikoma, MD, PhD  Department of Dermatology, University of California, San Francisco, 513 Parnassus Avenue, Room S-1268, San Francisco, CA 94143-0660, USA
akiikoma@kuhp.kyoto-u.ac.jp

Shigeki Inui, MD  Department of Regenerative Dermatology, Graduate School of Medicine, Osaka University, 2-2 (G5), Yamadaoka, Suita-shi, Osaka 565-0871, Japan
inui@r-derma.med.osaka-u.ac.jp

Akemi Ishida-Yamamoto, MD  Department of Dermatology, Asahikawa Medical College, Midorigaoka-Higashi 2-1-1-1, Asahikawa 078-8510, Japan
akemi@asahikawa-med.ac.jp

Satoshi Itami, MD, PhD  Department of Regenerative Dermatology, Graduate School of Medicine, Osaka University, 2-2 (G5), Yamadaoka, Suita-shi, Osaka 565-0871, Japan
itami@r-derma.med.osaka-u.ac.jp

Naotomo Kambe, MD, PhD  Department of Dermatology, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyō-ku, Kyoto 606-8507, Japan
nkambe@kuhp.kyoto-u.ac.jp

Yoko Kano, MD  Department of Dermatology, Kyorin University School of Medicine, 6-20-2 Shinkawa, Mitaka, Tokyo 181-8611, Japan

Ichiro Katayama, MD, PhD  Department of Dermatology, Integrated Medicine, Graduate School of Medicine, Osaka University, Suita-shi, Osaka 565-0871, Japan
katayama@derma.med.osaka-u.ac.jp

Robert Knobler, MD  Department of Dermatology, University of Vienna Medical School, Währinger Gürtel 18-20, 1090 Vienna, Austria
robert.knobler@meduniwien.ac.at

Sandra R. Knowles, RPH, BSc Phm  Drug Safety Pharmacist, Sunnybrook and Women’s HSC, 2075 Bayview Avenue, Room EG03, Toronto, ON, Canada M4N 3MS
sandra.knowles@sunnybrook.ca

Michal Kouba, MD  Institute of Hematology and Blood Transfusion, Charles University Prague, U Nemocnice 1, 12820, Prague 2, Czech Republic
michal.kouba@uhkt.cz

Liv Kraemer, MD, PhD  Department of Dermatology, Columbia University, New York Presbyterian Hospital, 161 Fort Washington Avenue, 12th Floor, New York, NY 10032, USA
Kenneth H. Kraemer, MD  DNA Repair Section, Basic Research Laboratory, National Cancer Institute, Building 37, Room 4002, Bethesda, MD 20892, USA Kraemer@nih.gov

Thomas Krieg, MD  Department of Dermatology, University of Cologne, Kerpener Straße 62, 50937 Cologne, Germany thomas.krieg@uni-koeln.de

George Kroumpouzos, MD, PhD, FAAD  9 Hawthorne Place, Suite 6D, Boston, MA 02114, USA george.kroumpouzos@gkderm.com

Thomas S. Kupper, MD  Department of Dermatology, Brigham and Women’s Hospital, 221 Longwood Avenue, Boston, MA 02115, USA nstrand@partners.org

Christine Labrèze, MD  Hôpital Pellegrin-Enfants, CHU de Bordeaux, Place Amélie Raba-Léon, 33076 Bordeaux Cedex, France christine.labreze@chu-bordeaux.fr

Annabelle Lozano, BS  7675 Phoenix Dr. #509, Houston, TX 77030, USA annabelle.lozano@bcm.edu

Thomas A. Luger, MD  Department of Dermatology, Clinical Neurodermatology, Ludwig-Boltzmann Institute for Cell Biology and Immunobiology of the Skin, University of Münster, Von-Esmarch-Straße 58, 48149 Münster, Germany luger@uni-muenster.de

Vandana Madkan, MD  6655 Travis, Suite 120, Houston, TX 77030, USA vmadkan@gmail.com

Alexander G. Marneros, MD  Department of Dermatology, The Irving Pavilion, Columbia Presbyterian Medical Center, 161 Fort Washington Avenue, 12th floor, New York, NY 10032, USA alexander_marneros@yahoo.com

Natalia Mendoza, MD, MSc  6655 Travis, Suite 120, Houston, TX 77030, USA nmendoza@ccstexas.com

Hans F. Merk, MD  Department of Dermatology, RWTH Aachen, Pauwelsstraße 30, 52074 Aachen, Germany hans.merk@post.rwth-aachen.de

Philip M. Meyers, MD  Columbia and Cornell University Medical Centers, Neurological Institute, 710 West 168th Street, New York, NY 10032, USA pmm2002@columbia.edu

Giuseppe Micali, MD  Department of Dermatology, University of Catania, Piazza S. Agata La Vetere 6, 95124 Catania, Italy cldermct@nti.it

Yoshiki Miyachi, MD, PhD  Department of Dermatology, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan ymiyachi@kuhp.kyoto-u.ac.jp
Yoshiko Mizukawa, MD  Department of Dermatology, Kyorin University
School of Medicine, 6-20-2 Shinkawa, Mitaka, Tokyo 181-8611, Japan

Robert L. Modlin, MD  Department of Dermatology, 52-121,
UCLA School of Medicine, 10833 Le Conte Avenue, Los Angeles, CA 90024, USA
rmodlin@mednet.ucla.edu

Takashi Mochizuki, MD, PhD  Department of Dermatology, Kanazawa Medical
University, Daigaku 1-1, Uchinada, Kahoku, Ishikawa 920-0293, Japan
mocizuki@kanazawa-med.ac.jp

Akimichi Morita, MD, PhD  Department of Geriatric and Environmental
Dermatology, Nagoya City University Graduate School of Medical Sciences,
1-Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan
amorita@med.nagoya-cu.ac.jp

Shin-ichi Moriwaki, MD  Department of Dermatology, Osaka Medical College,
2 – 7 Daigaku-cho, Takatsuki 569-8686, Japan
der002@poh.osaka-med.ac.jp

Carien M. Niessen, PhD  Department of Dermatology, University of Cologne,
Kerpener Straße 62, 50937 Cologne, Germany
carien.niessen@uni-koeln.de

Daniela Höller Obrigkeit, MD  Department of Dermatology, RWTH Aachen,
Pauwelsstraße 30, 52074 Aachen, Germany
daniela.hoeller@gmx.net

Jean-Paul Ortonne, MD  Service de Dermatologie, PC-Médicaux-Niveau 0,
Hôpital l’Archet 2, CHU de Nice, Route St., Antoine Gnestière,
06202 Nice Cedex 3, France
ortonne@unice.fr

Amy S. Paller, MD  Department of Dermatology, Northwestern University,
Feinberg School of Medicine, 676 N. St. Clair Street, Suite 1600, Chicago,
IL 60611, USA
apaller@northwestern.edu

David Pohlreich, MD  1st Department of Medicine, Charles University Prague,
U Nemocnice 1, 12820, Prague 2, Czech Republic
david.pohlreich@uhkt.cz

Rebecca G. Pomerantz, MD  Department of Dermatology,
University of Pittsburgh School of Medicine, BSTWR 1032, 3550 Terrace Street,
Pittsburgh, PA 15261, USA
rgp8@pitt.edu

Anja Potthoff, MD  Department of Dermatology and Allergology,
Ruhr University Bochum, Gudrunstraße 56, 44791 Bochum, Germany
a.potthoff@klinikum-bochum.de

Abrar A. Qureshi, MD  Department of Dermatology, Brigham and Women’s
Hospital, 221 Longwood Avenue, Boston, MA, USA
Heinrich Rasokat, MD  Department of Dermatology, University of Cologne, Kerpener Straße 62, 50937 Cologne, Germany  
hrasokat@uni-koeln.de

Alfredo Rebora, MD  Section of Dermatology, D, SEM, University of Genova, Viale Benedetto XV 7, I-16132 Genova, Italy  
rebdermo@unige.it

Laure Rittié, PhD  University of Michigan Medical School, 1301 E. Catherine, Ann Arbor, MI 48109-0609, USA  
lrittie@umich.edu

Franco Rongioletti, MD  Section of Dermatology, D, SEM, University of Genova, Viale Benedetto XV 7, I-16132 Genova, Italy  
franco.rongioletti@unige.it

Toshiaki Saida, MD, PhD  Department of Dermatology, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan  
tosaida@hsp.md.shinshu-u.ac.jp

Shinichi Sato, MD, PhD  Department of Dermatology, Nagasaki University, Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan  
s-sato@net.nagasaki-u.ac.jp

Richard K. Scher, MD, FACP  Department of Dermatology, 161 Fort Washington Avenue, IP 12th floor, New York, NY 10032, USA  
rs21@columbia.edu

Thomas Schwarz, MD  Department of Dermatology, University Kiel, Schittenhelmstraße 7, 24105 Kiel, Germany  
tschwarz@dermatology.uni-kiel.de

Robert A. Schwartz, MD MPH Dermatology, UMDNJ-New Jersey Medical School, 185 South Orange Avenue, Newark, NJ 07103-2714, USA  
roschwar@umdnj.edu

Neil H. Shear, MD  Department of Dermatology, University of Toronto, 2075 Bayview Avenue, Room M1737, Toronto, ON, M4N 3MS, Canada  neil.shear@sunnybrook.ca

Tetsuo Shiohara, MD  Department of Dermatology, Kyorin University School of Medicine, 6-20-2 Shinkawa, Mitaka, Tokyo 181-8611, Japan  
tpshio@kyorin-u.ac.jp

Robyn D. Siperstein, MD  10151 Enterprise Center Blvd, Suite 108, Boynton Beach, FL 33437, USA  
robyndsip@aol.com

347 N New River Dr E, Apt 2811, Fort Lauderdale, FL 33301, USA

Sonja Ständer, MD  Department of Dermatology, Clinical Neurodermatology, Ludwig-Boltzmann Institute for Cell Biology and Immunobiology of the Skin, University of Münster, Von-Esmarch-Straße 58, 48149 Münster, Germany  
sonja.staender@uni-muenster.de
Wolfram Sterry, MD  Department of Dermatology and Allergy, Charité University Medicine Berlin, Charitéplatz 1, 10117 Berlin, Germany wolfram.sterry@charite.de

Cecilia Svedman, MD  Department of Occupational and Environmental Dermatology, Malmö University Hospital, UMAS, Ing 73 (Entrance 45), S-205 02 Malmö, Sweden cecilia.svedman@skane.se

Hachiro Tagami, MD, PhD  Tohoku University School of Medicine, 3-27-1 Kaigamori, Aoba-ku, Sendai 981-0942, Japan hachitagami@ybb.ne.jp

Kazuhiko Takehara, MD, PhD  Department of Dermatology, Kanazawa University, Graduate School of Medical Science, 13-1 Takaramachi, Kanazawa, Ishikawa 920-8641, Japan takehara@med.kanazawa-u.ac.jp

Alain Taieb, MD  Hôpital Pellegrin-Enfants, CHU de Bordeaux, Place Amélie Raba-Léon, 33076 Bordeaux Cedex, France alain.taieb@chu-bordeaux.fr

Akan Tanaka, DVM, PhD  Laboratory of Veterinary Molecular Pathology and Therapeutics, Division of Animal Life Science, Graduate School, Tokyo University of Agriculture and Technology, 3-5-8 Saiwai-cho, Fuchu, Tokyo 183-8509, Japan akane@cc.tuat.ac.jp

Akiko Tanikawa, MD, PhD  Department of Dermatology, Keio University, School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan tanikawa@sc.itc.keio.ac.jp

Tadashi Terui, MD  Department of Dermatology, Nihon University School of Medicine, 30-1 Oyaguchi-Kamimachi, Itabashi-ku, Tokyo 173-8610, Japan terui@med.nihon-u.ac.jp

Yoshiki Tokura, MD  Department of Dermatology, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yhatanishi-ku, Kitakyushu 807-8555, Japan tokura@med.uoeh-u.ac.jp

Stephen K. Tyring, MD, PhD, MBA  6655 Travis, Suite 120, Houston, TX 77030, USA stephen.k.tyring@uth.tmc.edu

Peter C.M. van de Kerkhof, MD  Department of Dermatology, University Hospital Nijmegen, Postbus 9101, 6500 HB Nijmegen, The Netherlands, p.vandekerkhof@derma.umcn.nl

John J. Voorhees, MD  1910 Taubman Center, 1500 East Medical Center Dr., Ann Arbor, MI 48109-0314, USA voorhees@med.umich.edu
Dennis P. West, PhD  Department of Dermatology, Northwestern University, Feinberg School of Medicine, 676 N. St. Clair Street, Suite 1600, Chicago, IL 60611, USA
dwest@northwestern.edu

S. Mark Wilkinson, MD  Dermatology Department, Leeds Teaching Hospitals NHS Trust, Great George Street, Leeds, West Yorkshire LS1 3EX, UK
mark.wilkinson@leedsth.nhs.uk

Andreas Wollenberg, MD  Department of Dermatology and Allergy, Ludwig-Maximilian University, Frauenlobstraße 9-11, 80337 Munich, Germany
wollenberg@lrz.uni-muenchen.de

Bernhard Zelger, MD, MSc  Department of Dermatology and Venereology, Innsbruck Medical University, Anichstraße 35, 6020 Innsbruck, Austria
bernhard.zelger@i-med.ac.at

Christos C. Zouboulis, MD  Departments of Dermatology, Venereology, Allergology and Immunology, Dessau Medical Center, Auenweg 38, 06847 Dessau, Germany
christos.zouboulis@klinikum-dessau.de
Part

Introduction
The skin is the largest organ of the body and crucial for terrestrial life by providing a sturdy barrier toward the outside world. This barrier protects the organism from dehydration and prevents microbes and damaging agents from entering. The skin is challenged on a daily basis by a range of external insults, such as changes in temperature, UV light, and bacteria to thermal and mechanical injuries. Since in most cases, the skin is able to handle challenges without the occurrence of overt disease, this organ, by nature, must be an extremely versatile and dynamic tissue.

During evolution, the skin has gained a number of structural and functional features that allow it to react in an adequate manner to those external signals and injuries. Most importantly, the skin has developed ultrastructurally defined subcompartments that topically restrict external and internal damage.

The skin is composed of an epithelial and a mesenchymal compartment, the epidermis and the dermis, which are connected by a highly specialized extracellular matrix structure, and the basement membrane (Fig. 1.1.1). The dermis is resting on the subcutis, a fat layer that connects it to the fascia and the underlying muscles. These two compartments communicate extensively in various ways and at different levels, and this is crucial to establish, maintain, and restore homeostasis. During skin morphogenesis, this reciprocal interaction also determines the formation of the epidermal appendages, such as hair follicles, sweat glands, sebaceous glands, and nails, all structures that are required for normal skin function. Strong regional differences exist in the thickness and differentiation status of dermis and/or epidermis and the distribution of skin appendages. These variations are ontogenetically determined and form the basis for differential skin function required in various anatomical areas.

This chapter provides a general overview of, and introduction to, the cellular composition of the skin, the most important functions of the different cell types, and their particular contribution to the multifunctional skin barrier. Although it emphasizes several aspects more than others, this chapter does not aim at going extensively into details, and for the most part, uses citations of excellent and comprehensive reviews to refer to the reader who is interested to learn more on particular subjects. In addition, many chapters of this book will discuss the different aspects discussed here in light of skin disease.

### 1.1.1 Cellular Composition of the Epidermis

The epidermis and its appendages, hair follicles, sebaceous, and sweat glands form the physical barrier of the organism of the outside world. As a barrier, it
serves several important functions, both physical and immunological, which are reflected in the cell types and differentiation status that make up the epidermis.

Keratinocytes are the most predominant cell type in the epidermis and form the cornerstone of its overall structure and function. Epidermal keratinocytes balance lifelong self-renewal with a spatiotemporally strictly regulated terminal differentiation program, which ultimately leads to the formation of a dead, cornified, and water impermeable cell layer \([1, 2]\). This differentiation program generates four functionally different layers, each of which is characterized by a specific expression repertoire of intracellular and cell surface associated proteins (Fig. 1.1.1): (a) the basal layer or stratum basale consists of undifferentiated, proliferating cells. (b) the spinous layer or stratum spinosum contains the cells that have withdrawn from the cell cycle, migrated up from the basal layer while committing to differentiation. These cells also have switched keratins to synthesize a mechanically more stable keratin network. (c) The granular layer or stratum granulosum, dedicated to producing the majority of proteins, lipids, and enzymes for formation of the stratum corneum and (d) the stratum corneum, which is also known as the cornified layer, consists of corneocytes, composed of an insoluble cross-linked protein structure, the cornified envelope that serves as a scaffold for specialized lipids that form the intercellular lamina, thereby providing the epidermis with a water-impermeable barrier. Ultimately, this cornified layer is sloughed off in an only partially understood process called desquamation. The epidermal terminal differentiation program is a form of a programmed cell death that relates to the process of apoptosis, but is fundamentally different in key elements: e.g., cells are not phagocytosed and no activation of classical caspases occurs \([3, 4]\).

Different populations of stem and progenitor cells located in the basal layer of interfollicular epidermis (IFE) and in specific areas of hair follicles guarantee constant self-renewal under steady state conditions and sufficient plasticity for the fast replacement of lost tissue in case of injury. Morphogenetic signal pathways, such as Wnts, BMPs/TGF-\(\beta\), Notch and Hedgehogs, control the determination, renewal and maintenance of these stem cells \([5–10]\). The flexible...
balance between self-renewal and terminal differentiation is determined by the variable conditions of the extracellular environment.

Over the last decade, it has become clear that keratinocytes also actively contribute to the immunological barrier of the skin [11]. These cells produce antimicrobial peptides, such as defensins, and express Toll-like receptors on their cell surface, important for the control of innate immunity. In addition, upon disturbance of skin homeostasis, these cells secrete a wide range of cytokines and other growth factors that influence the innate and adaptive immune response.

Although over 90% of the epidermis consists of keratinocytes, other cells types, such as Langerhans cells, T-cells, melanocytes and Merkel cells, are present in the different layers (Fig. 1.1.1). These cells serve crucial specialized functions that contribute to epidermal homeostasis and to its restoration upon challenges of the epidermal barrier.

Merkel cells are postmitotic, neuroendocrine cells that produce a large number of cytokines and neuropeptides, form close connections with sensory nerve endings, and are mainly located in the basal layer of the epidermis. Ultrastructurally, these cells are characterized by dense core granules. Although these cells are the least well characterized cells in the epidermis, they are thought to have mechanosensory functions and contribute to the regulation of inflammatory responses [12, 13].

Langerhans cells are immature dendritic cells that form close contacts with keratinocytes and monitor microbial infection. Upon activation, these cells mature and migrate to draining lymph nodes where they present antigens to T-lymphocytes [14, 15]. Recent studies have revealed a novel functional aspect of Langerhans cells, showing that these cells not only contribute to immunostimulation, but also to immunosuppression [16].

The epidermis also contains a resident population of unique γδT-cells, which are in close contact with Langerhans cells and keratinocytes. These cells regulate skin inflammatory responses and play important roles in graft vs. host reactions in the skin [17]. By secreting different growth factors, they also play important roles in keratinocyte homeostasis and in wound repair [18]. Melanocytes produce melanin in specialized organelles, the melanosomes [19]. These cells are also in close contact with keratinocytes and this interaction determines melanin uptake by keratinocytes and thereby, skin pigmentation patterns [20]. The production and transfer of melanosomes is a complex and incompletely understood process, but plays a crucial role in the defense against the daily assault of UV light.

1.1.2 Cellular and Structural Composition of the Dermis

In contrast to the epidermis, the dermis is rich in extracellular matrix (ECM), and contains relatively fewer cells (Fig. 1.1.1). The upper or papillary dermis is characterized by loose connective tissue and a horizontal plexus of blood vessels, which are connected to a deep plexus located in the subcutis. The lower or reticular dermis makes up the major part of the dermis and mainly contains thick collagen bundles.

Fibroblasts are the predominant resident cells in normal dermis; they are responsible for producing and remodeling ECM. Even though these cells have been studied in depth in vitro with respect to their cellular adhesive, migratory, and differentiation properties, very little is known about their ability to differentiate in vivo. Fibroblasts in the papillary dermis differ from those in the reticular dermis with respect to growth potential and protein production, and both are different from hair follicle-associated fibroblasts [21]. Of interest, the concept of fibroblast heterogeneity applies not only to the skin but also to the entire human body, with fibroblasts in different anatomical sites and microenvironments being distinctly different in their gene expression programs and phenotypes [22]. The origin of dermal fibroblasts is an unresolved issue. They are thought to derive either from resident cells or from circulating mesenchymal progenitor cells that continually replenish the resident population. Modulating the differentiation of circulating or resident precursors is considered a novel approach for interfering with the development of fibrosis [23]. In some organ systems, fibroblasts were shown to originate from epithelial-to-mesenchymal transition (EMT); however, this origin has not yet been proven for the skin. Under the influence of TGF-β and topical mechanical forces, fibroblasts can “differentiate” into contractile myofibroblasts, driving wound contraction and the tissue response to tumors [24]. Fibroblasts as well as myofibroblasts actively participate in dermal homeostasis by contributing a plethora of growth factors.

Mast cells occur in virtually all vascularized tissues and are numerous in anatomical sites that are directly
exposed to the environment and easily identified by the presence of prominent cytoplasmic granules [25]. In the skin, they are frequently associated with blood vessels and appendages. Mast cells constitute an important cell type of the innate immune system and play an important role in inflammation and tissue remodeling. Their activation mainly occurs via the high affinity IgE receptor (FcεRI) or by contact with pathogens. Activated mast cells release an array of mediators e.g., histamine, proteases, and lipid metabolites, thereby causing extensive vasodilation, urticae, and itching, and are a rich source of growth factors. Although many released substances act as pro-inflammatory mediators, mast cells also seem to have immunosuppressive and anti-inflammatory roles through the release of IL-10 and TGF-β.

Other important constituents of the dermis are blood vessels and a lymphatic system, which are closely interconnected. The cutaneous microcirculation is organized as two horizontal plexuses, the upper one at the level of dermal papillae and the lower one at the dermal-subcutaneous junction. These are joined by paired ascending arterioles and descending venules. Microvascular endothelial cells supply nutrients to the skin and are essential for wound repair and the growth of tumors, and they regulate heat loss and temperature control. Depending on the size of the blood vessel and its location within the dermis, the endothelial tube is surrounded by up to several layers of smooth muscle cells or pericytes and by an outer basement membrane [26]. Endothelial cells and smooth muscle cells/pericytes form tight intercellular junctions with interdigitating processes, which together with the basement membrane control the distribution of biologically active molecules, mediators, or bioactive ECM fragments. Microvascular endothelial cells express a number of adhesion molecules for platelets and leukocytes to safeguard hemostasis and the transmigration of inflammatory and precursor cells from the circulation into the skin.

Much less is known about the lymphatic system, which drains protein-rich fluid from the extracellular space and transports immune cells from the skin to regional lymph nodes [27]. Lymph capillaries are lined by endothelial cells and are highly permeable due to the lack of a continuous basement membrane. The main difference between vascular and lymphatic endothelial cells in normal adult skin is the presence of VEGF receptor-1 or -2 on vascular endothelial cells, responding to the VEGF-A isoform, and VEGF receptor-3 on lymphatic endothelial cells, responding to VEGF-C. During tissue repair and tumor vascularization, this distinction is less clear and novel markers for the lymphatic system will help in the analysis.

The major part of the dermis is the connective tissue, composed of structural proteins and nonstructural elements produced predominantly by fibroblasts. This ECM provides structural support, organization and orientation to tissues. The structural elements are composed of collagens, elastin, fibrillins, fibronectin and other high molecular weight glycoproteins, which are members of smaller or larger protein families. They are large modular molecules assembled from a limited set of modules or domains, which have biological activity on their own. Most ECM genes have arisen by duplication of genes already present in ancestral organisms. The ECM proteins are embedded in a so-called ground substance of proteoglycans, which supply hydration and elasticity. Interaction between the different macromolecules builds a large macromolecular network [28–30].

One of the less appreciated, but not less important, functions of the ECM is the retention of growth factors such as TGF-β [31, 32]. Adequate stimulation or proteolytic activity can liberate the mediators and topically restrict their activity; this quick adaptive response is critical, for example, in inflammation.

Apart from exerting biological functions such as promoting migration or proliferation as entire ECM proteins, fragments cleaved off from them have gained attention for their own and have distinct properties, which may differ from the parental molecule [33]. One classic example is endostatin with antiangiogenic activity, which is cleaved off from the basement membrane collagen XVIII.

Probably, the largest ECM protein family is that of the collagens (Table 1.1.1), which exist in 28 different

<table>
<thead>
<tr>
<th>Table 1.1.1 Collagen types in the skin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dermis</strong></td>
</tr>
<tr>
<td>Fibril-forming collagens</td>
</tr>
<tr>
<td>I, III, V</td>
</tr>
<tr>
<td>FACITS (fibril-associated collagen with interrupted triple helix)</td>
</tr>
<tr>
<td>XII, XIV, XVI</td>
</tr>
<tr>
<td>Microfibrillar collagen</td>
</tr>
<tr>
<td>VI</td>
</tr>
<tr>
<td><strong>Basement membrane collagens</strong></td>
</tr>
<tr>
<td>Ubiquitous collagens</td>
</tr>
<tr>
<td>IV, XVIII</td>
</tr>
<tr>
<td>Anchoring fibril collagen</td>
</tr>
<tr>
<td>VII</td>
</tr>
<tr>
<td>Anchoring filament collagen</td>
</tr>
<tr>
<td>XVII</td>
</tr>
<tr>
<td>Endothelial basement membranes</td>
</tr>
<tr>
<td>VIII</td>
</tr>
<tr>
<td><strong>Epidermal/transmembrane collagens</strong></td>
</tr>
<tr>
<td>XIII, XVII, XXIII</td>
</tr>
</tbody>
</table>
types [34]. All have a similar structure with a characteristic triple helix, which can vary considerably in length. The fibril-forming collagens I, III and V make up most of the net weight of the dermis and represent the principle tensile element. The interstitial connective tissue also harbors the microfibrillar collagen VI and the fibril-associated collagen XIV. Collagen IV is a network forming molecule that is an essential constituent of the dermo-epidermal basement membrane. Collagen VII is the molecular component of the anchoring fibrils, which connect the basement membrane to the dermis.

Next to secreted collagens, there are unusual, transmembrane, collagens [35]. Interestingly, several of these unusual collagens are subject to ectodomain shedding by metalloproteases, resulting in the release of the extracellular domain. These collagens can thus exist in two functionally potentially very different protein forms. Although the functional significance is unclear currently, this mechanism allows cells to switch rapidly from a cell surface (adhesive) receptor to a secreted form that can serve as an ECM component. One of the best studied examples is collagen XVII, which is an important cellular component of hemidesmosomes in epidermal keratinocytes. It was initially discovered as one of auto-immune antigens in bullous pemphigoid, hence its alternative name BP180. Recently, a novel variant of collagen VI [36] was reported as potential molecular target of atopic dermatitis [37].

1.1.3 Basement Membranes

The epidermis and dermis cooperate in the formation of a highly specialized ECM structure, the basement membrane zone (BM), which physically separates these two compartments. The BM zone consists of a highly complex network of interconnecting ECM proteins, the key components being collagen IV, laminin, nidogen and proteolycans [38–40]. The skin basement membrane zone is characterized by auxiliary structures, the anchoring complexes, which consist of adhesion structures called hemidesmosomes (see below), anchoring filaments and anchoring fibrils. The anchoring filaments are mainly made up of Laminin 5, the major laminin isoform present in basement membranes of the skin and a crucial adhesive substrate for basal keratinocytes. Laminin-5 physically links the epidermis to collagen VII, the molecular constituent of the anchoring fibrils, which form the mechanical connection of the basement membrane to the underlying dermis. The importance of the anchoring complex in the maintenance of skin integrity is underscored by skin blistering diseases that are either caused by genetic mutations in one of these protein constituents of the basement membrane or by the production of auto-antibodies against several components [41–43].

1.1.4 Cell–Matrix and Cell–Cell Adhesion in the Skin

Intercellular and cell–matrix adhesion are crucial for cellular communication and play important roles in skin homeostasis and in the response to skin challenges. Cell adhesion is mediated by a large variety of cell adhesion receptors that can be subdivided into several different families. The most prominent of these are the integrin family of cell–matrix and cell–cell receptors, the cadherin superfamily of intercellular adhesion receptors, the IgG family of cell–cell and cell–matrix receptors, the selectins and the proteoglycan receptor family. Upon adhesion, most of these receptors cluster into specialized junctional structures that are associated with the cytoskeleton (Fig. 1.1.2). These structures not only have important adhesive functions but also provide the cell with spatial landmarks important for localized signaling. Indeed, for most adhesion receptors, it is now clear that they not only connect cells to their environment but also, by connecting to signaling molecules, can communicate signals from the cell to its environment (so called inside-out signaling), and from the environment to the cell (outside-in signaling) [44].

Intercellular junctions are most prominent in keratinocytes and endothelial cells (Fig. 1.1.2). However, dermal fibroblasts do form gap junctions and specialized forms of adherens junctions, which can be established over relatively long distances. Intercellular Junction formation is also dynamically regulated upon activation of dermal fibroblasts. In addition, intercellular junctions are crucial for dermal vascular integrity. Dynamic intercellular adhesion also plays a crucial role in the interaction of immune and inflammatory cells with other cell types when skin integrity is perturbed. Four different types of intercellular junctions characterize the epidermis:
1. Desmosomes consist of desmosomal cadherins that are linked to the keratin filament system through specialized cytoskeletal adapter proteins, such as plakoglobin, plakophilins and the plakin desmoplakin. In the skin, desmosomes are not only found in the epidermis but also in vascular endothelia, where they form an intermixed structure with adherens junctions, called syndesmosomes. Although desmosomes show an ultrastructurally similar appearance throughout the epidermis, they have distinct molecular compositions that depend on the differentiation status of the keratinocytes, and most likely contribute specific functions [45]. For example, corneocytes are connected by a specialized variant, the corneodesmosome. Their importance for epidermal integrity is underscored by the existence of genetic and auto-immune skin blistering diseases, which are characterized by mutations in, or antibodies against, desmosomal components [46]. Next to their importance in providing mechanical strength to epidermal intercellular cohesion, novel functions have emerged for desmosomal components in the regulation of differentiation, survival, and growth.

2. Tight junctions form size and ion specific barriers in epithelia and vascular endothelial cells. In the epidermis, functional tight junctions are present in the granular layer. Tight junctions consist of two different four transmembrane spanning protein families, the occludins and claudins that link to actin via several different linker molecules e.g., the scaffolding proteins ZO-1/2. Differential expression of claudins provides tight junctions found at different sites with their size and ion specificity and, thereby, determine the tightness of the epithelial and vascular barrier [47, 48]. For keratinizing epithelia, it was originally thought that the secretion and deposition of a cross-linked protein–lipid barrier obviated the need for a tight junction barrier in such tissues, even though tight junctional proteins were identified in the epidermis. The first functional evidence that a tight junction component is required for barrier function in epidermis came from claudin-1 knockout mice, which showed severe water...
loss due to impaired barrier function of the stratum granulosum. Subsequently, a dense network of strands resembling tight junctions was shown to be present in the stratum granulosum of human epidermis. It is now widely accepted that tight junctions form a critical part of the barrier in the upper viable layer of stratifying epithelia [47]. Improper function of tight junctions most likely contributes to human skin diseases, since claudin-1 mutations have been found to be associated with a rare form of ichthyosis [46].

3. Adherens junctions link cellular adhesive contacts, mediated by classical cadherins and the IgG subfamily of nectins, to the actin cytoskeleton. Both adhesion molecules can form a dynamic link to the cytoskeleton by interacting with actin binding proteins and with regulators of actin dynamics [49]. Their importance of adhesion in the skin is underscored by the recent observation that autoantibodies to E-cadherin results in skin blistering diseases [50]. In addition, cell contacts of keratinocytes with T-cells, Langerhans cells and melanocytes are mediated by E-cadherin [51]. Dynamic differential classical cadherin expression in the basal layer also contributes to epidermal and hair follicle morphogenesis [52]. This is further emphasized by the observation that mutations in P-cadherin underlie hair disorders as well as rare forms of ectodermal dysplasia [53, 54]. In mice, it was shown that epidermal E-cadherin is crucial for functional tight junctions in the granular layer, thereby regulating epidermal barrier function [47].

4. Gap junctions are crucial structures for intercellular communication by forming pores that allow the passage and exchange of small molecules between adjacent cells [55]. Connexin proteins constitute the molecular basis of the pores. Their importance for skin function is demonstrated by connexin mutations that underlie a number of inherited skin related diseases, including Vohwinkel syndrome and ichthyosis, and palmoplantar keratoderma related entities [46, 56].

Cell–matrix adhesion structures consist of integrin based hemidesmosomes and focal adhesions (Fig. 1.1.2). Hemidesmosomes anchor epidermal keratinocytes firmly to the underlying basement membrane and are absent in other skin cell types. Focal adhesion like structures can be observed both in the dermis and epidermis. Integrins are heterodimeric adhesion receptors, consisting of an α and β subunit, the composition of which determines ligand specificity. Integrins are found on almost all cell types of the body where they function not only as cell–cell or cell–matrix adhesion receptors, but also communicate signals from the inside to the outside of the cell and vice versa. As such, they perform crucial functions in the regulation of connective tissue metabolism, epithelial morphogenesis and homeostasis, vascular function, and immune system. They form the most important group of cell–matrix receptors in the skin.

Hemidesmosomes, or half desmosomes, resemble desmosomes at the ultrastructural and functional level, in that they show a similar organization, and by connecting to keratin filaments, are crucial structures for mechanical stability. Nevertheless, their molecular composition is very different, consisting of the integrin α6β4 and the previously mentioned collagen XVII (formerly known as BPAG1) as adhesion receptors and several cytoskeletal linker molecules of the plakin family, such as plectin and BP230 [57]. The β4 subunit is unique among the integrin β subunits because of its long cytoplasmic domain that, unlike the other actin-linked β subunits, links α6β4 to intermediate filaments. Hemidesmosomes are crucial for the integrity of the skin, since mutations have been found in each of its known components, all of which lead to skin blistering diseases [42, 58].

The β1 and αv integrin subfamilies provide the scaffold of focal adhesions, which recruit a variety of cytoskeletal and signaling proteins, the most prominent ones being talin, vinculin, kindlins, the focal adhesion kinase (FAK), and integrin linked kinase (ILK) [59]. These structures are crucial for skin homeostasis, since they contribute to a wide variety of functions on the different skin cells. Many of these are important for skin homeostasis, as underscored by the loss of β1-integrins in the epidermis of mice, resulting not only in the formation of microblisters, but also in proliferative defects and skin inflammation [60]. Other functions become more important when the skin is challenged. For example, α2 integrins regulate vascularization during wound healing [61]. Although focal contacts as a structure have not been identified in the skin in vivo, related structures are most likely important, as emphasized by the mutations in different focal contact components that underlie skin blistering related diseases [46].

A recently emerging theme is that adhesive junctions may not only be crucial for tissue integrity and serve as clustering sites for signaling molecules, but
may also regulate communication with the nucleus at two different levels. First, it is now clear that many of the cytoskeletal linker proteins associated with adhesive junctions can also translocate to the nucleus where they regulate transcription [44, 62]. In addition, several cytoskeletal linker proteins also interact with components of the nuclear matrix, thereby potentially linking cell adhesion to nuclear positioning and shape changes, which can affect general transcriptional activity [63].

1.1.5 Molecular Basis of the Epidermal Barrier

The physical epidermal barrier is built up by two physically separated compartments: the tight junctions present in the uppermost viable layer, the stratum granulosum and the stratum corneum, which consists of a lipid and protein component, often referred to as “brick and mortar” [64, 65]. Tight junctions and the stratum corneum may cooperate in the formation of a functional barrier in stratifying epithelia. For example, overexpression of claudin-6 in the upper layers of the epidermis or epidermal deletion of the membrane anchored serine protease (CAP)1/Prss8 induced barrier defects that involved alterations in both tight junctions and stratum corneum. Although the underlying mechanisms are unknown, they may involve the coordinated regulation of both barriers by signal molecules such as IKK1 and retinoic acid receptor signaling [66]. In simple epithelia, tight junctions form a fence, thereby separating the apical membrane domain from the basolateral membrane domain. Since formation of the stratum corneum depends on the fusion of lamellar bodies and keratohyalin granules with plasma membranes at the transition between stratum granulosum and stratum corneum layers, it is tempting to speculate that the specific occurrence of tight junctions in the stratum granulosum regulates targeting of protein and lipid vesicles directly towards the “apically localized” stratum corneum (reviewed in [47]).

The importance of site specific expression of keratins is best reflected in the identification of mutations in, until now, 19 keratins in skin related diseases, most of which are associated with skin blistering [69]. These keratin related diseases not only emphasize their crucial importance in providing regional and site specific mechanical strength to epithelia, but also provide intriguing hints for other keratin related functions independent of structure. Keratin mutations identified in both mice and human are associated with pigment defects, albeit the underlying mechanisms by which keratins regulate epithelial pigmentation patterns are mostly unclear. Studies in mice have also uncovered roles of keratins in determining the onset of apoptosis crucial for hair follicle cycling and in the regulation of protein synthesis and cell size. Recently, a fascinating link has been established between focal adhesion formation and keratin filament assembly, suggesting that the different adhesion structures and their associated cytoskeletal networks communicate directly to provide mechanical strength to cells (reviewed in Gu et al., 2007). The plakin
family of cytoskeletal binding proteins may perform key functions in these processes, since they can interact with both actin and intermediate filaments [63].

Keratins form the core components of the corneocytes, the anucleate cells of the stratum corneum [70]. This requires bundling of the keratin filaments, in which the late differentiation protein filaggrin plays an important role in the bundling of keratins and in the formation of the cornified envelope that forms the outer layer of the corneocytes. At the late steps of cornification, filaggrin is processed into free hygroscopic amino acids that act as the natural moisturizing factors of the skin. Indeed, mutations in filaggrin underlie ichthyosis variants and are also associated with atopic dermatitis, indicating its crucial importance not only in stratum corneum formation, but also in skin hydration [71]. Filaggrin is initially produced in the granular layer as a huge precursor, profilaggrin, which aggregate to form the characteristic keratohyalin granules of this layer. The cornified envelope consists of a dense network of proteins, mostly loricrin, involucrin and cornifin, which are tightly cross-linked to each other by enzymes such as transglutaminases [3]. Specialized desmosomes, so-called cornodesmosomes, connect corneocytes. A crucial step of desquamation is the proteolytic cleavage of these cornodesmosomes. The intercellular space between corneocytes is filled by the lipid lamellae, a specialized structure of lipids crucial for epidermal water barrier function [72, 73].

An important aspect of cornification and the subsequent process of desquamation is the spatiotemporal activation and inhibition of proteases, cross linkers and lipid enzymes [74]. Although not well understood, these complex processes are balanced by inhibitors and activators of these enzymes and are at least partially regulated by gradients in pH and Ca²⁺-concentrations. The importance of proper spatiotemporal activation is stressed by diseases caused either by inappropriate activation or inhibition of these different enzymes due to e.g., lack of inhibitors or activators [75, 76].

### 1.1.6 Cellular Communication Within the Skin

In recent years, it has become increasingly clear that the different skin cell types have a profound functional influence on each other, and that an extensive cellular cross-talk regulates cell proliferation, differentiation, and coordinates the cellular and immunological responses to environmental challenges. Data generated in the recent past have resulted in a change of paradigm in understanding skin homeostasis and substantial number of skin diseases. It is now clear that keratinocytes and fibroblasts not only represent the scaffold of the epidermis and dermis, but are also actively involved in the regulation of e.g., the innate and adaptive immune system [77]. They do so by secreting a large number of different mediators to communicate with endothelial cells and with inflammatory cells during wounding or disease conditions. These include pro-inflammatory cytokines, such as IL-1, IL10, and IL-6, antibacterial peptides, and growth factors such as VEGF or TGF-β. In turn, the activity of these cells and their extracellular mediators profoundly influence the differentiation status of the keratinocytes and fibroblasts, thereby determining their response when the multifunctional skin barrier is challenged [78, 79]. An important modulatory role in skin communication is provided by the ECM that not only serves as an important structural scaffold but also, by interacting with cells and many of the cytokines and growth factors, alters their functional activity. Together, these new findings and insights have led to the realization that the primary cause of skin diseases associated with barrier dysfunction and inflammation can reside in keratinocytes and fibroblasts with a secondary contribution of classical inflammatory cell types, activated through cellular communication. In addition, such primary defects in the skin can affect homeostasis of other organs, resulting in associated diseases in these organs.

### 1.1.7 Concluding Remarks

The last decade has brought a tremendous progress in the cell biology of the skin and thereby contributed to a better understanding of human skin diseases, as many of the examples mentioned in the following chapters exemplify. What many of these studies clearly revealed, regardless of whether one is looking from a fibroblast, endothelial cell, a keratinocyte, or immune cell point of view, is the extensive communication that occurs between cells and compartments of the skin. These new insights and findings can now be used to identify the primary and secondary events that are still unknown.
for many of the skin diseases, and to develop new therapies for these diseases.

Acknowledgments We would like to thank all our colleagues in the Department of Dermatology and other departments within the University of Cologne for many stimulating discussions on skin biology. Because of limited space and broadness of the subject, we were, for the most part, only able to cite reviews and unfortunately had to leave out many of the original studies that have contributed to the tremendous progress in understanding the cell biology of the skin. For this, we like to apologize to our colleagues.

References

corneocyte proteins in these disorders. Adv Dermatol 23: 231–256
The skin is endowed with the capacity to generate immune responses, which gave rise to the term “skin-associated lymphoid tissues” (SALT) [22]. The classical immune response, also referred to as the adaptive immune response, is characterized by specificity that is due to immunological memory (specific immunity) [16]. In addition, there exists another more primitive defense system, which acts in a rapid but nonspecific manner [4]. The latter is called innate immunity. Both types of responses can be generated in the skin. Adaptive immune reactions in the skin, however, are not always protective and can also be harmful in nature, e.g., allergic or autoimmune reactions. Numerous skin diseases are caused by T lymphocytes and are therefore immunologically mediated.

### 1.2.1 Innate Immunity

Innate immune responses are characterized by the lack of immunologic memory. These immune reactions are less complicated than adaptive responses and therefore developed earlier in evolution [13]. Nevertheless, failures in these “primitive” immune responses may be associated with severe, even fatal health problems. Essential components of the innate response are neutrophils, eosinophils, natural killer cells, mast cells, cytokines, complement, and, as recently discovered, antimicrobial peptides. The innate response is rapid and less controlled than the adaptive immune response.

### 1.2.2 Activation of Innate Responses via Toll-Like Receptors

Innate immunity recognizes invading microorganisms and induces a host defense response. The molecular mechanisms that underlie innate immune recognition remained quite unclear until recently. It is now recognized that a family of pattern recognition receptors...
exists, which mediate responses to pathogen-associated molecular patterns (PAMP) that are conserved among microorganisms. Human Toll-like receptors (TLR) are one such family of pattern recognition receptors. TLR4 recognizes lipopolysaccharide and TLR9 bacterial CpG DNA sequences. The signaling pathway of TLR is highly homologous to that of the receptor for interleukin-1 (IL-1). It has been recently recognized that dendritic cells express several of the TLR. Upon activation of these receptors by microbial components, dendritic cells mature and present pathogen-derived antigens to naïve T cells, thereby inducing an adaptive immune response. Therefore, TLR are regarded as molecules, bridging the gap between innate and adaptive immunity [1]. This crosstalk between innate and adaptive immunity was further confirmed by the observation that TLR8 signaling appears to control the function of regulatory T cells [17].

1.2.3 Protection from Cutaneous Infection by Antimicrobial Peptides

To cope with an environment that is full of microorganisms, plants and invertebrates produce a variety of highly effective antimicrobial proteins. Vertebrate epithelia can also function as a source of such antimicrobial proteins. Accordingly, it was demonstrated that human epithelia, including the epidermis, secrete such antimicrobial peptides, and thereby, exhibit the capacity to mount an innate chemical defense. The first antimicrobial peptide isolated from human skin was human β-defensin-2 (hBD-2) [9]. Constitutive expression of these peptides may protect skin from bacterial superinfection, as recently demonstrated for psoriasis, which effectively protects from infection with E. coli [5]. Many of the peptides can be induced by bacteria and bacterial products or by proinflammatory cytokines. Bacteria may induce antimicrobial peptides via TLR, but this is certainly not the only mechanism. Enhanced expression of these peptides in psoriasis may explain the rare frequency of superinfections in this disease, whereas the expression appears to be downregulated in atopic skin, which is quite frequently superinfected [15].

1.2.4 Monocytes/Macrophages

Macrophages are phagocytic cells derived from blood-borne monocytes. Macrophages carry receptors for carbohydrates that are usually not expressed on vertebrate cells, e.g., mannose. Through this recognition pathway, macrophages can discriminate between “foreign” and “self” molecules. Furthermore, macrophages possess receptors for antibodies and complement. Hence, coating of microorganisms with antibodies and/or complement enhances phagocytosis. After phagocytosis, the microorganisms are exposed to a variety of toxic intracellular molecules, including superoxide anions, hydroxyl radicals, hypochlorous acid, nitric oxide, lysozyme, and antimicrobial cationic proteins. Macrophages can also present processed antigens to T and B cells. However, their T cell stimulatory capacity is much less effective than that of other dendritic cells.

1.2.5 Adaptive Immunity

The characteristic features of an adaptive immune response are its specificity and its improvement with each successive encounter with the same antigen due to the accumulation of a kind of memory [4, 16]. A crucial event during the generation of an adaptive immune response is antigen presentation.

1.2.6 Antigen-Presenting Cells of the Epidermis

Within the epidermis, Langerhans cells (LC) are the relevant antigen-presenting cells (APC). Ultrastructurally, LC are specifically identified by the existence of rod-shaped organelles, termed Birbeck granules. For a long time, the function of Birbeck granules was a matter of debate. A recently identified Ca²⁺-dependent lectin with mannose-binding specificity, called Langerin, was found to be associated with Birbeck granules and even to induce formation of Birbeck granules [24]. Hence, induction of Birbeck granules appears to be a consequence of the antigen-capture function of Langerin, allowing routing of antigen into
1.2 Immune Mechanisms

CD1a is the most useful marker for detecting human LC, since within the epidermis, it is exclusively expressed on LC, both in normal and inflamed tissues [20]. This does not apply for HLA-DR antigens, since they can also be expressed on keratinocytes in inflamed skin, and thus are not suitable for detecting LC under these conditions. In addition, LC were found to express the high-affinity IgE receptor (FcεRI) that was initially thought to be exclusively expressed on mast cells and basophils [21, 25]. The density of LC decreases with age and is reduced in chronically UV-exposed skin [20].

To initiate sensitization, antigens must be presented to lymphocytes by APC [2]. LC play a crucial role in the presentation of antigens, which are generated in or enter the skin. Initial evidence for this assumption was provided by the observation that contact sensitization could not be induced in skin areas that were devoid of LC or in which LC had been depleted, e.g., by ultraviolet radiation [23]. However, other APC must be able to replace LC, since transgenic mice in which LC are completely depleted via the diphtheria toxin receptor technique reveal a diminished, but not abrogated, sensitization response [3]. In another study using a similar model, the sensitization response was not inhibited at all [11]. While the experimental model of these two studies allows a short-term inducible ablation of LC in vivo, another knock-out model yielding constitutive and durable absence of epidermal LC was created [10]. Unexpectedly, these mice also have an enhanced sensitization response, suggesting that LC may exert a kind of regulatory function. This “LC paradigm” proposes that LC may act in both ways: may be tolerogenic when they present antigens under steady-state noninflammatory conditions and sensitizing upon stimulation by inflammatory mediators [12, 14].

For the MHC class II-dependent antigen presentation to T cells dendritic cells, including LC, B cells and monocytes/macrophages are required. MHC class II-associated antigen presentation primarily targets exogenous (and rarely endogenous) antigens [8, 26, 27]. Exogenous antigens are taken up via macro- or micro-pinocytosis or via receptor-mediated endocytosis. One example for the latter is the DEC-205 receptor (CD205), which guides antigens into deeper endocytic vesicles containing MHC class II molecules. As a consequence of this unique intracellular targeting, antigens endocytosed by the DEC-205 receptor stimulate respective T cells up to 500-fold better than antigens taken up by pinocytosis or by other receptors. The finding has fostered speculations on the use of this receptor to target antigens to DC for induction of antigen-specific immune responses, e.g., against melanoma antigens or leishmania antigens. Finally, the MHC class II molecule with the bound antigen peptide is expressed on the cell surface allowing antigen recognition by T cells carrying the appropriate T cell receptor.

1.2.7 Contact Allergy

Allergic contact hypersensitivity (CHS) is highly relevant for dermatologists, since it is the pathogenic basis for allergic contact dermatitis, one of the most frequent inflammatory dermatoses. CHS has always been highly relevant for basic immunologists as well, since numerous immunologic discoveries have been made utilizing the model of CHS [6].

Most of the contact allergens are low-molecular weight chemicals, which after penetrating into the skin, have to couple with host proteins to be able to act as full antigens. This process is called haptenization, and therefore, these low-molecular allergens are called haptens. Upon epicutaneous application to a naïve host, LC take up the hapten, process it and migrate towards the regional lymph nodes, where the antigen is presented to naïve T cells. During the emigration, LC convert from a “resting” into an “activated” functional state. This process is initiated by keratinocytes, which secrete inflammatory cytokines as a result of hapten application, and is possibly also due to direct effects of haptens on LC themselves. LC activation is associated with an induction of cytokine secretion (interleukin [IL]-1β, IL-6, IL-12, chemokines), enhanced cell surface molecule expression (MHC class I and II molecules, adhesion molecules, costimulatory molecules), antigen uptake, processing, and presentation [6].

Activation and induction of emigration of LC seems to be dependent on the capacity of haptens to induce IL-1β secretion in LC. Induction of IL-1β is an immediate effect of epicutaneous hapten application and appears to be specific for haptens, since it is not observed with irritants or tolerogens. In addition,
other cytokines including chemokines, tumor necrosis factor (TNF-α), and GM-CSF may also contribute to LC activation and migration. Hence, the hapten itself, through its capacity to induce a specific cytokine pattern, seems to be the initial trigger factor that activates LC and induces sensitization. However, it is important to note that LC are not absolutely required for sensitization, since other cutaneous APC, such as dermal dendritic cells, may also contribute to priming of naïve T cells, after the epicutaneous application of haptens [3].

Presentation of the hapten in the regional lymph nodes causes activation of naïve T cells carrying the appropriate T cell receptor and finally results in the generation of effector cells. In contrast to other types of delayed type hypersensitivity responses, which are mediated by CD4+ T cells, most haptens induce a T cell response in which mainly CD8+ effector T cells are involved [6]. In addition, T cell populations are induced which downmodulate the CHS response. These inhibitory T cells, that were initially called suppressor T cells, appear to belong to the group of regulatory T cells. The balance between effector T cells and regulatory T cells seems to depend on the dose of the antigen applied, since application of extremely low doses of the hapten does not result in sensitization, but rather in tolerance [19].

T cells that have been primed in the draining cutaneous lymph nodes express the skin homing marker cutaneous lymphocyte antigen (CLA) and, thereby, exhibit the capacity to enter the skin [18]. These T cells become activated when they encounter their relevant hapten presented by LC within the skin. However, in contrast to the sensitization phase, antigen presentation can now be taken over by cells other than LC including keratinocytes, dermal mast cells and macrophages, all of which are readily capable of presenting antigens at least in an MHC class I-restricted fashion [6]. Alternatively, inflammatory cells that infiltrate the site of hapten application very early during the response may function as APC.

The earliest histopathologic findings during a CHS response are mast cell degranulation, vasodilatation, and an influx of neutrophils, followed by mononuclear and T cells. However, the pathophysiologic events that result in allergic contact dermatitis are clearly T cell-dependent, since T cell-deficient mice are unable to mount a CHS response. Yet low doses of hapten that are sufficient to stimulate hapten-specific T cells have been found to be insufficient to elicit a CHS response. This indicates that the elicitation of a CHS response requires, in addition to hapten-specific recognition, some type of proinflammatory stimulus that appears to be provided by the hapten itself and to be quite dose-dependent [7].

1.2.8 Keratinocytes are Important Regulators of Skin Immunity

Although LC are undoubtedly the major immunologic cells within the epidermis, keratinocytes are also vital contributors to the generation of a cutaneous immune response. Due to their close physical proximity, keratinocytes can affect LC by the expression of specific surface molecules. In addition, keratinocytes are able to provide signals to LC in a contact-independent manner via the release of soluble mediators, in particular, cytokines, eicosanoids and neurohormones.

For decades, keratinocytes were regarded as primitive cells endowed only with the capacity to produce keratins to provide a mechanical barrier to the outside. Therefore, it was quite surprising when it was discovered that keratinocytes could secrete immunologic and inflammatory mediators. The first cytokine identified as being released from keratinocytes was IL-1. Subsequently, keratinocytes were shown to have the capacity to secrete a multitude of soluble mediators. These included pro- and anti-inflammatory, immunomodulatory, and immunosuppressive cytokines. Among the immunomodulatory mediators released by keratinocytes are IL-1, IL-6, TNF-α, IL-8 and other members of the chemokine family. Anti-inflammatory activity can be mediated by keratinocytes via the release of IL-10, IL-1 receptor antagonist and TGF-β. Keratinocyte-derived immunomodulatory mediators include IL-7, IL-12, IL-15, IL-18, IL-19, IL-20, GM-CSF, G-CSF, and M-CSF, while cytokines with immunosuppressive properties include IL-10 and TGF-β. Especially, IL-10 has been successfully developed for the systemic treatment of psoriasis. Of interest is also IL-15, which appears to strengthen antimicrobial immunity. Nevertheless, there are cytokines that are certainly not produced by keratinocytes, e.g., IL-2, IL-4 and interferon-γ.

Although some cytokines are produced in tiny quantities by keratinocytes, such low concentrations may suffice to exert an effect in the topical microenvironment. Any perturbation of the skin may induce the release of these mediators by the keratinocytes.
For example, UV radiation is a potent inducer of cytokine production and release. Chemicals with the potential for inducing either irritant or allergic reactions also cause cytokine release from keratinocytes.

In addition to cytokines, keratinocytes release prostaglandins and leukotrienes. Leukotriene B4 is a potent chemoattractant. Prostaglandin E2 possesses both inflammatory and immunosuppressive properties. The erythema caused by UV radiation is partially mediated by prostaglandin E2. There is additional evidence that the skin, and especially keratinocytes, can function as a source of neuropeptides, in particular, substance P and pro-opiomelanocortin (POMC)-derived peptides including alpha-melanocyte stimulating hormone.

Acknowledgments Many important aspects and references could not be included due to space restrictions. We apologize to the respective authors. This work was supported by the Deutsche Forschungsgemeinschaft (DFG, SFB 617/A2; SCHW1177/1-1/1-2; SFB 293/B8; BE1580/7-1), Interdisciplinary Clinical Research Center (IZKF) Münster, and the Medical Faculty (IMF), University of Münster, Germany.

References

20. T. Schwarz and S. Beissert


1.3.1 Basic Principles and Definitions

**Adverse drug effects:** The unintended consequences associated with normal doses of administered drugs.

**Area under the curve:** The plot of plasma concentration of drug against time after drug administration.

**Bioavailability:** The amount of unchanged drug reaching the bloodstream following administration by any route.

**Clinical pharmacology:** The scientific discipline dedicated to the study of drugs in humans.

**Cytochrome P-450:** Enzyme superfamily functioning as terminal components of the microsomal mixed function mono-oxygenase system that catalyzes the biotransformation of predominantly lipophilic molecules such as drugs and xenobiotics (chemical compounds that are foreign to a living organism) into inactive, more water-soluble species that can be more readily excreted from the body.

**Drug:** Chemical substance used to diagnose, treat, or prevent disease, or to enhance physical or mental well-being.

**Drug–drug interaction:** The altered response to one drug when administered concomitantly with another drug. This may involve an increase or a decrease in the pharmacologic action of either drug, or it may be an adverse effect that is not normally associated with either agent.

**Drug tolerance:** The decreased response to a drug such that larger doses are required to achieve the same pharmacologic effect.

**Drug toxicity:** The adverse effects of drugs.

**Drug transporters:** Expressed in many tissues and play key roles in drug absorption, distribution, and excretion.

**Half-life:** The time required for 50% of the dose of an administered drug to be eliminated from the body.

**Idiosyncratic reactions:** The unintended consequences of administered drugs generally unrelated to the administered dose.

**Pharmacology:** The scientific discipline that addresses all aspects of drugs including their origin (natural or synthetic), chemical structure, pharmacokinetics (absorption, distribution, metabolism, excretion), and pharmacodynamics (biochemical and physiological mechanisms of action, correlating drug structure and function).

**Pharmacodynamics:** The study of the relationship between drug concentrations and drug effects.

**Pharmacogenetics:** The study of the relationship between individual gene variants and variable drug effects.

**Pharmacogenomics:** The study of the relationship between variants in a large collection of genes, up to the whole genome, and variable drug effects.

**Pharmacokinetics:** The study of the relationship between drug dose and drug concentrations (often as a function of time) in plasma or tissue.

**Polymorphisms:** DNA variants that are common, often defined as greater than 1% in a given population. Polymorphisms can be in coding regions or more commonly in noncoding regions and often vary by ethnicity. The most common type of polymorphism is a change in
one nucleotide in a DNA sequence, referred to as a single nucleotide polymorphism (SNP). The functional consequences of most polymorphisms are unknown.

*Pro-drug:* A compound that must undergo chemical transformation before becoming an active pharmacological agent: a precursor of an active drug.

*Side effects:* Drug actions that are distinct from the intended therapeutic effect.

### 1.3.2 Pharmacokinetics: Absorption

Absorption defines drug transport from its site of administration to the systemic circulation (bloodstream). Factors that influence plasma membrane drug transport include its molecular structure, its solubility at the site of absorption, its lipid:water partition coefficient, tissue vascularity, and the relative membrane solubility of its ionized and unionized isoforms [5].

Drug transport across lipid-rich cell membranes occurs primarily by passive diffusion that is directly proportional to the concentration gradient across the membrane and the drug’s lipid solubility. In general, ionized water-soluble polar drugs penetrate membranes poorly, whereas nonpolar lipid-soluble drugs quickly reach steady-state concentrations on both sides of the membrane. Most drugs are weak acids or weak bases and depending upon pH exist in solution as a combination of ionized and nonionized species. The nonionized form is usually lipid-soluble and able to penetrate the lipid-rich membrane while the ionized form cannot penetrate, and is not absorbed.

In addition to passive diffusion, drugs can move across membranes, such as the blood–brain barrier and the gastrointestinal mucosa by carrier-mediated transport. This usually requires a reversible reaction between the substance being transported and components of the membrane. The membrane component is the “carrier.” This form of drug transport is saturable and is subject to competitive inhibition (multiple agents competing for the same carrier).

There are two forms of carrier-mediated transport, active transport and facilitated diffusion. For example, the transfer of drugs or their metabolites into urine generally occurs by active transport, whereas glucose transport into most cells occurs by facilitated diffusion. Active transport requires the direct expenditure of energy, whereas facilitated diffusion does not. Active transport permits movement of drugs against a concentration gradient, but facilitated diffusion does not.

### 1.3.3 Bioavailability of Orally Administered Drugs

The bioavailability of a given dose of an orally administered drug may be less than 100% due to incomplete absorption or first-pass elimination (in either the gastrointestinal tract or the liver). First-pass effect refers to hepatic or gastrointestinal metabolism of certain orally administered drugs that pass through the liver or gut before reaching the systemic circulation. One approach of eliminating first-pass effects is to administer drugs transdermally or sublingually.

### 1.3.4 Percutaneous Absorption

The skin is a complex membrane that performs many physiological functions such as metabolism, synthesis, temperature regulation, and excretion. Its upper layer, the stratum corneum, is considered to be the main barrier to the percutaneous penetration of exogenous materials. This barrier is also important in the maintenance of water within the body, as well as in the absorption of pharmaceutical and other agents. There are several categories of pharmaceutical products, which are targeted to the skin or utilize the skin as a port of entry into the body, and these include transdermal drug delivery systems (patches), gels, creams, ointments, lotions as well as subcutaneous implants, and dermal vaccinations. In contrast to the traditional oral route, the use of transdermal drug delivery by-passes first-pass metabolism of the liver, the acidic environment of the gastrointestinal tract, and problems of absorption in the stomach, which often contains food, resulting in erratic and pulsed delivery of drugs into the intestine and variability in plasma concentration-time profiles. As with other routes of delivery, transport across the skin is also associated with several disadvantages, the main drawback being that not all drugs are suitable candidates. A number of physicochemical parameters have been identified (such as molecular
weight) that influence the diffusion process, and variations in permeation rates can occur between different skin models, patients, different races, and between young and old. The major challenge is overcoming the resistance of the skin to permeation in a reversible and nondamaging manner, as well as the design of therapeutically effective topical and transdermal formulations [5, 7, 10].

Molecules can penetrate the skin by three routes: through intact stratum corneum, through sweat ducts, or through the sebaceous follicle. The surface of the stratum corneum presents more than 99% of the total skin surface available for percutaneous drug absorption, and passage through this outermost layer is the rate-limiting step for percutaneous absorption. The major steps involved in percutaneous absorption include the establishment of a concentration gradient, which provides a driving force for drug movement across the skin, release of drug from the vehicle (partition coefficient), and drug diffusion across the layers of the skin (diffusion coefficient). Preferable characteristics of topical drugs include low molecular mass (≤600 Da), adequate solubility in oil and water, and a high partition coefficient. Except for very small particles, water-soluble ions and polar molecules do not penetrate intact stratum corneum. The relationship of these factors to one another is summarized in the following equation

\[ J = C_{\text{veh}} \cdot K_m \cdot D/x, \]

where \( J \) = rate of absorption; \( C_{\text{veh}} \) = concentration of drug in vehicle; \( K_m \) = partition coefficient; \( D \) = diffusion coefficient; and \( x \) = thickness of stratum corneum [5].

### 1.3.5 Pharmacokinetics: Distribution

Distribution defines the movement of an absorbed drug from the systemic circulation into various tissue compartments. While in the circulation, drugs can exist in their free state, that is unbound to plasma proteins, or they may bind to plasma proteins. Only free unbound drug is able to distribute to tissues. Tissue distribution is limited by cardiac output and regional perfusion.

The drug’s concentration gradient across the plasma membrane, defined as the diffusible fraction (free drug that is lipid-soluble and nonionized) determines the rate of distribution to tissues. Tissue perfusion may also influence the concentration gradient if the drug is poorly absorbed.

One measure of drug distribution is known as the volume of distribution (Vd), defined as that volume of bodily fluid into which a drug dose is dissolved. Therefore, if the administered dose is known and if the serum level (concentration) can be measured, then we can calculate a volume of distribution.

The central volume of distribution (Vc) is a hypothetical volume into which an administered drug initially distributes. This includes circulating blood and those tissues with high perfusion such as the heart, lung, and kidneys. The peripheral volume of circulation (Vp) is the sum of all tissue spaces outside the Vc. All drugs initially distribute into the smaller Vc before distributing into the Vp. Thus the Vd = Vc + Vp.

Vd is defined as L/kg. A drug with a large Vd binds to peripheral tissues (e.g., fat) whereas a drug with a small Vd exists primarily in the circulation, or in body fluids.

### 1.3.6 Pharmacokinetics: Metabolism

First order kinetics defines a chemical reaction in which the rate of the reaction depends on the concentration of one agent, and is proportional to the amount of the reactant. The body handles most drugs by first order kinetics such that the rate of absorption and elimination is directly proportional to their concentration. The higher the blood concentration, the faster it is eliminated. A second type of kinetics is known as zero order kinetics or Michaelis-Menten kinetics in which the rate of elimination is independent of concentration.

### 1.3.7 Half-Life

Half-life is the time required for 50% of the dose of an administered drug to be eliminated from the body. In reality, this is a measurement of the time it takes for the drug’s plasma concentration to be reduced by 50%. This is also known as the plasma elimination half-life (t\( \frac{1}{2} \)). There is great interindividual variation in t\( \frac{1}{2} \), often related to alterations in hepatic and renal function.
The half-life can be determined from a plasma elimination curve or can be calculated. Half-life varies directly with Vd and inversely with clearance, as expressed by the equation \( t_{1/2} = \frac{0.693 \times Vd}{Cl} \). Half-life offers a good estimate of the time required to reach steady state after drug administration, but may not necessarily provide useful information regarding its actual duration of action, or its elimination from the body.

### 1.3.8 Area Under the Curve (AUC)

The AUC is the plot of plasma concentration of drug against time after drug administration. The AUC is of particular use in estimating bioavailability of drugs and total drug clearance. The ratio of the AUC after oral administration of a drug formulation to that after the intravenous injection of the same dose to the same subject is used during drug development to assess a drug’s oral bioavailability.

### 1.3.9 Clearance

Clearance measures the body’s ability to eliminate a drug. Half-life is inversely proportional to clearance. Various disease states as well as the degree of plasma protein binding will influence clearance and Vd.

Lipid-soluble drugs are cleared primarily through the liver whereas water soluble drugs (and water-soluble metabolites of lipid-soluble drugs) are cleared through the kidneys. The balance of hepatic and renal clearance of both the parent drug and any active metabolites must be understood to prescribe wisely.

Drug and xenobiotic metabolism define the process, whereby lipid-soluble, pharmacologically active compounds are converted to water soluble inactive metabolites that are more readily excreted from the body [1, 3, 8, 9]. In general, these metabolites have less pharmacological activity as compared to the parent compound. And yet, in some instances, drug metabolites may actually be more toxic than the parent compound. Metabolic activation of some drugs ("prodrugs") may be required for their pharmacological activity. Furthermore, metabolic activation of certain environmental polycyclic hydrocarbon carcinogens may be a critical step in the initiation of cancer.

In general, there are two types of drug metabolizing enzymatic reactions known as Phase I and Phase II reactions.

The most important enzyme family involved in Phase I reactions is the heme-protein family known as cytochrome P-450 (CYP). These belong to a superfamily that are the terminal components of the microsomal mixed function mono-oxygenase system that catalyze the conversion of a range of predominantly lipophilic molecules such as drugs and xenobiotics (chemical compounds that are foreign to a living organism) into inactive more water-soluble species that can be more readily excreted from the body. A common mechanism is the insertion of an atom of molecular oxygen into these substrates. CYPs are also involved in various synthetic and catabolic reactions of endogenous biologically active substances including fatty acids, vitamins, steroids and prostaglandins [1, 3, 5, 8, 9]. To date, 18 families of CYPs and 43 subfamilies of the same have been identified in humans (http://drnelson.utmem.edu/CytochromeP450.html) [8]. Most drug-metabolizing CYPs are members of the CYP 1–4 gene families, which number 35 (61%) of the total 57 putative functional CYP genes in humans. Phase I reactions usually convert the parent drug to more polar metabolites by variable processes including, among others, oxidation, reduction, hydrolysis, and dealkylation [3, 8]. Phase I metabolites possess variable pharmacological activity.

Phase II reactions conjugate the drug or its phase I metabolite(s) to endogenous water-soluble substrates, such as glucuronic acid and sulfuric acid. Phase II products are usually pharmacologically inactive. All conjugation reactions except glucuronidation are catalyzed by soluble (nonmembrane bound) enzymes.

All tissues express drug metabolizing enzymes although hepatic microsomal enzyme systems account for the biotransformation of the majority of drugs [8]. Drug metabolism also occurs in tissues functioning as environmental interfaces including the skin, the lungs, and the gastrointestinal tract [2, 3, 5].

Clinical studies showing inherited differences in drug effects have given rise to the field of pharmacogenetics [13]. It has been known for decades that human subjects show bimodal distributions of plasma drug levels, following administration of a standard drug dosage. These results show that human populations can be divided into poor metabolizers (PM) and
extensive metabolizers (EM). Further complicating the issue is that epigenetic phenomena such as DNA methylation patterns, covalent modifications of histones and chromatin, and RNA interference can influence patterns of xenobiotic metabolism.

Variation in the N-acetyltransferase gene divides people into “slow acetylators” and “fast acetylators.” Differential acetylation rates alter the half-lives and blood concentrations of such important drugs as isoniazid (anti-tuberculosis) and procainamide (antiarrhythmic), with resultant diminished efficacy or augmented toxicity.

Numerous factors affect the rates of drug metabolism. Enzyme induction defines the process, whereby exposure to certain drugs and xenobiotics results in accelerated biotransformation, diminished efficacy, and a resultant reduction in unmetabolized drug [8, 11]. In contrast, if the metabolic rate decreases the potential for drug, toxicity may be increased. Enzyme inhibition occurs when multiple drugs utilize the same isozyme and compete for the same enzyme receptor site. The more potent inhibitor will predominate, resulting in decreased metabolism of the competing drug. For most drugs, this can lead to increased serum levels of the unmetabolized entity, leading to a greater potential for toxicity.

For example, CYP3A4 is a CYP isozyme that metabolizes cyclosporine. Co-administration of cyclosporine with a CYP3A4 inhibitor such as nefazodone decreases the dosage requirement for cyclosporine. Similarly, concomitant administration of the CYP3A4 inhibitors, erythromycin, and grapefruit juice raised serum levels of the non-sedating antihistamines, terfenadine, and astemizole, leading to potentially fatal cardiac arrhythmias [11].

### 1.3.10 Pharmacokinetics: Excretion

The kidneys are the most important organs for elimination of drugs and their metabolites. Substances excreted in feces are either unabsorbed orally administered drugs or their metabolites excreted in bile. Excretion of drugs in milk is important because of potential toxicity in nursing neonates. Pulmonary excretion is of minor importance for most drugs.

Urinary excretion of drugs and/or metabolites requires three processes: glomerular filtration, active tubular secretion, and passive tubular reabsorption. The amount of drug entering the tubular lumen by glomerular filtration is dependent on its fractional plasma protein binding and the glomerular filtration rate (GFR). In the proximal renal tubules, organic anions and cations enter the glomerular filtrate by active, carrier-mediated tubular secretion (e.g., penicillin). In the proximal and distal tubules, the nonionized forms of weak acids and bases undergo net passive reabsorption, assuming that a concentration gradient exists between the renal tubular fluid and perfusing blood.

Many metabolites formed in the liver are excreted into the intestinal tract via the bile. They may be excreted in feces or may be enzymatically converted to the active drug and be reabsorbed (termed enterohepatic circulation).

### 1.3.11 Drug Transporters

Drug–drug interactions may involve transporters [6, 16, 18, 19]. The potential involvement of both transporters and metabolic enzymes responsible for a drug’s disposition complicates efforts to predict drug–drug interactions in vivo. Multiple human drug transporters have been identified that are expressed at the apical or basal side of epithelial cells in various tissues including the skin [2, 15]. Most drug transporters belong to two superfamilies, ABC (ATP-binding cassette) and SLC (solute-linked carrier), including both cellular uptake and efflux transporters. P-glycoprotein (abbreviated as P-gp or Pgp) is a well-characterized human ABC-transporter of the MDR/TAP subfamily. It is extensively expressed in numerous cell types including keratinocytes. P-gp is also called ATP-binding cassette sub-family B member 1 (ABCB1), multiple drug resistance 1 (MDR1), and PGY1. P-glycoprotein has also recently been designated CD243 (cluster of differentiation 243). Organic anion transport protein (OATP) also known as SLC is a second organic anion transporter family [18].

Analogous to drug–drug interactions mediated by CYP enzymes, co-administration of a drug that is an inhibitor or an inducer of a drug transporter may affect the kinetics of a second drug substrate for the same transporter. For example, digoxin is a P-gp substrate that is eliminated mainly unchanged via renal and biliary excretion. Its AUC has been found to increase with co-administration of several P-gp inhibitors such as...
quinidine, itraconazole, and atorvastatin, and decrease with co-administration of P-gp inducers such as rifampin and St. John’s wort [19]. Another recent example suggests a transporter-mediated interaction between rosuvastatin, a known substrate for OATP1B1 (gene: SLC01B1), and cyclosporine, identified as an effective inhibitor of the same transporter. When rosuvastatin was coadministered with cyclosporine in heart transplantation patients, its AUC increased sevenfold. These examples underscore the fact that polymorphisms in drug-metabolizing enzymes alone may not adequately account for the individual variation in absorption, distribution, and elimination of drugs, and that transporters may play a role in these processes.

### 1.3.12 Pro-Drugs

Because of the skin’s resistance to the percutaneous absorption of many drugs, efforts have been made to develop alternative strategies to enhance drug delivery through the skin. The use of prodrugs is essentially a process in which physical or chemical modification of the penetrating drug molecule provides a mechanism for altering skin permeability to enhance rate of absorption [4, 12, 17]. The prodrug strategy, in effect, a manipulation of the drug-skin and drug-vehicle interactions. A particularly good example of the utility of this approach is illustrated by the topical retinoid, tazarotene. It is well recognized that both water and lipid solubilities, and a balance of the two, are crucial to maximize the percutaneous absorption of topically applied agents. Tazarotene in its active carboxylic acid form (tazarotenic acid) is esterified to a more lipophilic ethyl ester, which still maintains adequate water solubility. Esterases in the skin remove the ethyl ester which maximizes penetration of the parent drug that is rapidly converted back to the less lipophilic tazarotenic acid [12]. Tazarotenic acid undergoes further metabolism to its sulfoxide and other polar metabolites that are rapidly eliminated via both urinary and fecal pathways, with a terminal half-life of about 18 h. Reduced systemic half-life of the parent drug results from introducing a metabolically labile sulfur group that is susceptible to rapid oxidative inactivation, and thus prevents accumulation in tissues. Thus, tazarotene is not only a carboxylic acid prodrug with enhanced skin permeability, but is also a soft drug with enhanced systemic metabolism. This type of design provides two major advantages simultaneously: enhanced skin penetration and augmented systemic biotransformation to minimize tissue accumulation of any systemically absorbed drug.

### 1.3.13 Pharmacogenetics

Pharmacogenetics is the study of interindividual variations in the DNA sequence that are related to drug responses such as efficacy and toxicity. Pharmacogenomics is the study of the variability of the expression of individual genes relevant to disease susceptibility, as well as drug response at the cellular, tissue, individual, or population level [13, 18]. Pharmacogenetics considers retrospectively one or at most a few genes associated with an observed therapeutic outcome, whereas pharmacogenomics generally studies whole-genome variations prospectively.

### 1.3.14 Pharmacogenetics and Adverse Drug Reactions

Current clinical interest in pharmacogenetics focuses on polymorphisms in drug metabolism, with a particular emphasis on improving drug safety. Pharmacogenetic testing may provide useful tools for improving drug safety and efficacy. Comparison of drugs, most commonly implicated in adverse drug reactions, correlates remarkably well with drugs metabolized by enzymes with known polymorphisms.

The enzyme thiopurine methyltransferase (TPMT) metabolizes 6-mercaptopurine and azathioprine, two thiopurine drugs used for treating autoimmune diseases. In people with deficient TPMT activity, thiopurine metabolism utilizes alternative biotransformation pathways, one of which yields a metabolite that is toxic to the bone marrow [14]. One in 300 people have two variant alleles that lack TPMT activity; these people need only 6–10% of the standard dose of the drug, and, if treated with full dose, are at risk for severe bone marrow suppression, secondary to elevated plasma levels of 6-thioguanine nucleotide. Testing for the TPMT polymorphisms associated with azathioprine toxicity is now available and can be useful in preventing toxic reactions to this drug in susceptible patients.
# References


1.4.1 Introduction

The adaptive immune system mounts specific responses to defend the body from invading pathogens that have overcome the primary defense mechanisms of the nonspecific innate immune system. Lymphocytes, specialized leukocytes with surface receptors that enable recognition of a specific antigen, are the primary effector cells of the adaptive immune system. In particular, B cells (B lymphocytes) mediate the humoral immune response. Each B cell targets a single pathogen by secreting an antibody that binds to the microbe, targeting it for destruction. In contrast, cell-mediated immunity involves the activation of multiple processes to destroy intracellular pathogens and lyse infected cells, in a process mediated by T cells. T cells stimulate cytokine secretion, leading to activation of destruction pathways. Immune responses are the result of the coordinated action of numerous cellular and molecular effectors.

Immunomodulation contributes to the pathogenesis of a vast array of diseases. In cancer, uncontrolled cell growth circumvents or overcomes the checks of the immune system. The goal of immune-modifying therapies for cancer is to effect antitumor responses through amplification of innate immune reactions against cancer or through delivery of tumor-specific immune effectors. In autoimmune diseases, immune cells fail to distinguish endogenous antigens from foreign antigens, leading to pathologic immune activity in which the body attacks its own tissues. Traditional therapy for autoimmune diseases is management with immunosuppressive corticosteroid agents, which block the production of inflammatory cytokines. Increasingly, highly specific immunomodulatory agents are being used to suppress particular biochemical reactions underlying autoimmune pathogenesis. B cells, T cells, and the proinflammatory cytokine TNF-α are the primary immune effectors targeted by current immunomodulatory medications for dermatologic diseases.

1.4.2 B Cell Targeting

1.4.2.1 Rituximab

Rituximab is a chimeric human–murine monoclonal antibody that targets CD20, an antigen expressed by both normal and malignant B cells. By binding to CD20, rituximab reduces the number of circulating B cells in multiple pathways, including antibody-dependent cellular cytotoxicity, complement-mediated cell lysis, and induction of apoptosis [1]. Because CD20 is not expressed by most plasma cells, antibody production is maintained after treatment with rituximab.
and normal B cells are later regenerated by hematopoietic stem cells. The net result is a reduction in the number of neoplastic B cells without a concomitant decrease in serum immunoglobulin levels [2].

The primary clinical application of rituximab is for treatment of CD20-positive, B cell, non-Hodgkin’s lymphoma (NHL), where it is usually given as a course of 4–8 weekly, 375 mg/m² intravenous infusions. In cutaneous oncology, rituximab has been used to treat primary cutaneous B cell lymphoma (PCBCL), for which the traditional first-line treatment paradigms are radiation for localized lesions and polychemotherapy for diffusely spread disease. A potential role of rituximab as a first-line alternative is suggested by numerous reports of dramatic responses to its use in PCBCL patients [3]. In a recent study comparing intravenous and intralesional rituximab therapy in eight PCBCL patients with a follow-up period of 18–24 months, neither of the two patients who received intravenous rituximab relapsed, and new lesions that developed in four of the six patients receiving the drug intralesionally responded to subsequent injections. No major adverse events were reported [4]. Randomized, controlled clinical trials are needed to confirm the therapeutic potential of rituximab in PCBCL.

In addition to its use in PCBCL, rituximab has been successful in treating a number of autoimmune disorders of the skin. There are many reports of rituximab use in refractory autoimmune bullous diseases, including pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, bullous pemphigoid, and epidermolysis bullosa acquisita, with almost all patients showing clinical improvement on rituximab after failure of other treatment modalities [5]. Nine of eleven pemphigus vulgaris patients treated with rituximab plus intravenous immune globulin had rapid resolution of lesions and a mean remission of 31.1 months, and all patients were able to taper off the use of any other immunosuppressant medications before completing the rituximab regimen [6]. A number of reports describe the successful use of rituximab to treat systemic lupus erythematosus, dermatomyositis, and chronic graft versus host disease (GVHD) [7]. Most of the data on the tolerability of rituximab comes from clinical trials in NHL patients and suggests a low toxicity profile, with the majority of adverse events being mild-to-moderate and infusion-related [8].

1.4.2.2 Mycophenolate Mofetil

Mycophenolate mofetil (MMF) exerts its therapeutic effect by inhibiting inosine monophosphate dehydrogenase, an enzyme important for the de novo synthesis of guanosine nucleotides. Lymphocytes rely on this pathway for DNA and RNA synthesis, whereas other cell types can acquire purines through alternative pathways. Thus, MMF selectively inhibits the proliferation of B and T cells, leading to suppression of cell-mediated immune responses. MMF is usually taken orally twice per day, with a total daily dose of 2–3 g for adults and up to 2 g for children.

While the FDA-approved use of MMF is for prevention of organ transplant rejection, a variety of off-label uses in dermatologic conditions have been described. MMF has been used successfully to treat psoriasis, with 77% of 18 patients completing a prospective open-label trial showing significant improvement on the psoriasis area and severity index (PASI) [9]. The efficacy of MMF as therapy for atopic dermatitis (AD) has also been studied. In a retrospective analysis, 17 of 20 AD patients improved within 4 weeks of receiving MMF; ten patients had AD remission and were able to discontinue use of the drug, while seven patients maintained control of the disease with continued use of MMF [10]. Previous studies of MMF in AD have shown mixed success [11].

Patients with autoimmune bullous diseases have responded to treatment with MMF. In a study of 42 pemphigus sufferers, 71% of pemphigus vulgaris patients and 45% of pemphigus foliaceus patients had a complete remission of disease, with a median time of 9 months to remission [12]. Successful outcomes with MMF therapy have also been reported in bullous pemphigoid, paraneoplastic pemphigus, cicatricial pemphigoid, linear IgA bullous dermatosis, and epidermolysis bullosa acquisita [11]. Use of MMF has produced clinical responses in systemic lupus erythematosus and other lupus variants, including improvement of cutaneous manifestations [13]. MMF may be useful in a variety of other diseases affecting the skin, including dermatomyositis, scleroderma, GVHD, lichen planus, pyoderma gangrenosum, and sarcoidosis [11].

Most of the information on the tolerability and safety of MMF comes from studies of its use in organ transplantation [14]. The most common adverse events
are nausea, vomiting, diarrhea, and abdominal cramps. In contrast to many other systemic immunosuppressive agents, MMF use is not associated with liver, kidney, or cardiovascular toxicities.

1.4.3 T Cell Targeting

1.4.3.1 Alefacept

Alefacept is a fully human fusion toxin that binds to the CD2 antigen on the surface of T cells, blocking its interaction with LFA-3 on antigen-presenting cells. This blockade leads to the inhibition of T cell activation and proliferation and substantially reduces the number of circulating CD4+ memory effector T cells, a subset of lymphocytes that plays an important role in the pathogenesis of psoriasis.

Alefacept is approved for the treatment of moderate-to-severe chronic plaque psoriasis and is given as a series of 12–24 weekly doses of either 15 mg (intramuscularly) or 7.5 mg (intravenously). According to current recommendations, CD4 count should be monitored in patients taking alefacept with baseline and weekly checks, and the medication should not be administered when the CD4 count drops below 250 cells/μL.

Clinical trials of alefacept in psoriasis have shown a high rate of major clinical response. Among patients receiving two 12-week courses of intravenous alefacept in a 553-subject Phase III study, 40% had a PASI reduction of 75% or greater, and 71% had a PASI reduction of 50% or greater [15]. Intramuscular dosing was also shown to be effective in a large Phase III study (n = 507) [16]. Numerous other trials of alefacept have demonstrated its efficacy in psoriasis, with approximately 70% of patients achieving a clinically significant response after 24 weeks of treatment [17].

A low incidence of minor side effects, including headache, upper respiratory tract problems, and pruritus, have been reported in patients receiving alefacept, and the drug has not been associated with the development of major infections or malignancies [18]. Alefacept therapy is contraindicated in patients with HIV, since further depletion of CD4 cells in these patients may worsen the HIV course.

1.4.3.2 Efalizumab

Efalizumab is a humanized monoclonal antibody that binds to CD11a, the α subunit of LFA-1, blocking the interaction between LFA-1 and intracellular adhesion molecule 1. This leads to the inhibition of key signaling pathways involved in T cell activation and the movement of T cells from the circulation into the skin.

Efalizumab, approved for the treatment of moderate-to-severe chronic plaque psoriasis, is usually given as a weekly subcutaneous dose of 1 mg/kg, following an initial dose of 0.7 mg/kg. In phase III studies enrolling a total of 1,651 psoriasis patients, 27.8% of patients receiving 12 weekly doses of subcutaneous efalizumab achieved a PASI improvement of 75% or greater, and 56.1% had a PASI improvement of 50% or greater [19]. Over 3,500 psoriasis patients have received efalizumab in Phase I, II, and III trials, with significant disease improvement experienced by the majority of patients, and some rapid responses observed within the first 2–4 weeks of beginning treatment [20]. Psoriasis usually returns with cessation of efalizumab, however, and maintenance therapy or alternation with other treatments is generally needed to control the disease.

Efalizumab has a favorable tolerability profile. The majority of adverse events are mild-to-moderate, occur within 2 days following the first and second injections, and include headache, chills, fever, nausea and myalgia [21]. Based on current data, treatment with efalizumab does not appear to increase malignancy risk [22].

1.4.3.3 Cyclosporin

Cyclosporin, an inhibitor of the phosphatase calcineurin, is a lipophilic polypeptide that binds to the intracellular protein cyclophilin (cyclophilin A). This cyclosporin-cyclophilin complex binds to calcineurin, inhibiting the dephosphorylation of nuclear factors important for gene transcription leading to T cell activation.

Cyclosporin was the first T cell-targeting medication to be given to organ transplant patients and has since been used to treat inflammatory diseases of the
bowel, joints, and skin. The medication is usually given as one or two oral doses totaling up to 5 mg/kg/day. In dermatology, cyclosporin is currently approved for treatment of severe psoriasis and AD. Of 181 patients with severe psoriasis who received a 16-week course of 5 mg/kg/day cyclosporin, 86% had a 70% or more reduction in the body surface area affected by the disease [23], and some patients who have failed treatment with all other agents have had their psoriasis controlled with cyclosporin [24]. Cyclosporin is also highly effective for AD in both adults [25] and children [26]. However, in both psoriasis and AD, most patients experience disease relapse when cyclosporin use is discontinued. Case reports and case series describe the success of cyclosporin therapy in a variety of other dermatoses, with the most significant responses seen in pyoderma gangrenosum, lichen planus, Behcet’s disease, and the autoimmune bullous diseases [24].

The commonly reported side effects of cyclosporin therapy are minor to moderate gastrointestinal problems and headache. Significantly, the use of cyclosporin carries well-known risks of renal toxicity and hypertension, which limit the suitability of the drug for long-term use. Therefore, cyclosporin is sometimes used as a component of a rotational therapy regimen. Owing to its tendency to produce rapid regression, cyclosporin is particularly useful for treating acute dermatosis flares.

**1.4.3.4 Tacrolimus**

Like cyclosporin, tacrolimus exerts its therapeutic effect by suppressing calcineurin activity, but the two drugs differ in structure and in their immediate targets. Tacrolimus is a fungus-derived macrolide lactone that binds to the immunophilin FKBP-12. By binding to calcineurin, the tacrolimus-immunophilin complex inhibits transcription pathways important for the T cell-mediated immune response.

While the primary clinical use of tacrolimus is for prevention of organ rejection, the topical form of the drug has dermatologic applications. Tacrolimus ointment is available in 0.03% and 0.1% formulations and is currently indicated as a second-line treatment for moderate-to-severe AD. In a meta-analysis of randomized controlled trials, 44% of AD patients receiving 0.1% topical tacrolimus had greater than 90% disease improvement, while 62% had at least 75% improvement. Tacrolimus 0.1% is as effective as hydrocortisone butyrate and more effective than hydrocortisone acetate for treating AD [27]. Additionally, significant responses to tacrolimus have been reported in a variety of inflammatory dermatoses besides AD, including psoriasis, seborrheic dermatitis, contact dermatitis, lichen sclerosus, and lichen planus [28].

Tacrolimus therapy is a good alternative to the long-term use of topical steroids, particularly on the thinner skin of the face. Since systemic absorption of topical tacrolimus is minimal, a low toxicity profile is expected, although the safety of long-term tacrolimus use has not yet been established. In clinical trials of topical tacrolimus, the most commonly reported side effects are skin irritation and skin burning [27].

**1.4.4 Tumor Necrosis Factor-α Targeting**

Tumor necrosis factor-α (TNF-α) is a cytokine that promotes inflammatory responses through its involvement in keratinocyte proliferation, adhesion molecule expression, and recruitment of immune cells to sites of inflammation [29]. Due to its proinflammatory role in immune signaling, TNF-α has been the target of multiple medications for inflammatory diseases of the joints, bowel, and skin. The monoclonal antibodies, infliximab and adalimumab, and the fusion protein, etanercept, exert their therapeutic effects by binding to TNF-α, preventing formation of TNF-α homotrimers, and blocking interaction with p55 and p75 cell surface receptors, and thus inhibiting the TNF-α-mediated inflammatory cascade. The features of these three TNF-α antagonists and their uses in diseases with cutaneous involvement are summarized in Table 1.4.1.

TNF-α is involved in normal immune responses, but is upregulated in the plasma and skin lesions of patients with psoriasis [30]. High levels of TNF-α are associated with high PASI scores, and a decrease in TNF-α levels is associated with clinical improvement following treatment [31]. Furthermore, since TNF-α inhibitors are effective therapy for a variety of inflammatory pathologies, they may be particularly useful for patients with multiple coincident autoimmune diseases. For example, psoriasis is more prevalent among individuals with inflammatory bowel disease, and a
TNF-α antagonist may serve as effective monotherapy for both conditions [32]. Similarly, inhibition of TNF-α is associated with improvements in both the articular and cutaneous symptoms of psoriatic arthritis patients [33].

### 1.4.4.1 Infliximab

Of the three currently available TNF-α antagonists, infliximab was the first to be developed and therefore has been most extensively studied. In a randomized, controlled 16-week trial of infliximab in psoriatic arthritis (n = 104), 65% of treated patients had significant joint improvements, and patients receiving infliximab had a mean PASI improvement of 86%. During a 50-week follow-up, joint and skin improvements were maintained with continued infliximab treatment [33]. In clinical trials of infliximab in uncomplicated moderate-to-severe psoriasis, a majority of patients have had substantial disease improvement [34, 35]. A number of case reports describe positive outcomes of infliximab therapy in Behcet’s disease, hidradenitis suppurativa, sarcoidosis, scleroderma, dermatomyositis, and SAPHO syndrome [36], and a randomized, controlled trial showed efficacy in pyoderma gangrenosum [37]. About 10% of patients develop antibodies to infliximab, where the likelihood of experiencing an infusion reaction is related to the development of an anti-infliximab antibody [38]. In a trial of infliximab in psoriasis, the most common side effects were headache, diarrhea, rash, and upper respiratory problems [35].

### 1.4.4.2 Etanercept

The efficacy of etanercept for psoriasis and psoriatic arthritis has been well documented in clinical trials. In a study enrolling 205 psoriatic arthritis patients, 70% of etanercept-treated patients met criteria for joint improvement after 24 weeks, and the mean PASI improvement at that time point was 47% [39]. In a phase III trial of etanercept in 583 psoriasis patients, a 50% or greater PASI improvement was achieved by 77% of patients receiving 50-mg injections twice/week for 12 weeks [40]. For treatment of the joint disease in psoriatic arthritis, 25-mg etanercept injections are given twice weekly, but in cases of moderate-to-severe concomitant psoriasis, 50 mg twice weekly injections are usually required to control the skin disease. In patients with psoriatic arthritis, joint symptoms often respond to etanercept within the first 2 weeks of therapy, while the time frame for psoriasis improvement is usually two months or longer. Cases of successful etanercept treatment have been described in pyoderma gangrenosum, scleroderma, dermatomyositis, and SAPHO syndrome, [36] and a randomized controlled trial showed improvement in the mucocutaneous manifestations of Behcet’s disease in etanercept-treated patients [41]. Etanercept is well-tolerated in most patients. The most common side effects are minor, and include injection site reactions, headaches, and dizziness.

### 1.4.4.3 Adalimumab

Adalimumab is the newest and least well-studied of the TNF-α targeting medications. Subcutaneous
adalimumab injections are usually given at a dose of 40 mg every other week, with an increase to weekly dosing in cases of severe refractory disease. At the 24-week time point of a randomized, controlled trial in 313 psoriatic arthritis patients, 58% of adalimumab-treated patients met criteria for joint response, and 59% had a PASI improvement of 75% or greater [42]. In a trial of adalimumab in moderate-to-severe psoriasis (n = 147), 53% of patients receiving the drug every other week and 80% of patients receiving weekly doses had a PASI improvement of 75% or greater after 12 weeks, and responses were sustained at week 60 [43]. Currently, there are few published case reports of off-label adalimumab use; positive outcomes have been described in sarcoidosis [44], Behcet’s disease [45], and hidradenitis suppurativa [46]. Adalimumab has a good tolerability profile; most side effects are minor and include injection site reactions, headache, nausea, and upper respiratory problems [47].

1.4.5 Other Targeting Pathways

1.4.5.1 Abatacept

Abatacept (CTLA4Ig) is a recombinant fusion protein of cytotoxic T lymphocyte antigen-4 (CTLA4) and immunoglobulin that acts by inhibiting the action of CD28, a T cell surface receptor that transduces signals leading to T cell activation and proliferation. Abatacept acts as a competitive inhibitor of CD28 by binding to its natural ligands (CD80 and CD86) on antigen-presenting cells, inhibiting their interaction with CD28, and thus suppressing CD28-mediated T cell activity.

Abatacept, currently approved as a second-line treatment for moderate-to-severe rheumatoid arthritis, is given as a 10-mg/kg intravenous infusion every 2–4 weeks. Abatacept has shown efficacy in multiple Phase III clinical trials in patients with rheumatoid arthritis, including patients with active disease despite a previous course of methotrexate [48] or anti-TNF-α therapy [49]. In clinical trials of abatacept in rheumatoid arthritis, 51.8% of treated patients experienced an adverse effect that was thought to be related to abatacept use, and 3% had a serious adverse event [50]. The most common side effects were headache, upper respiratory tract infection, nasopharyngitis, and infusion reactions. Concurrent anti-TNF-α treatment increases the toxicity of abatacept therapy, particularly the likelihood of infection, without contributing a significant therapeutic benefit [51]. Data describing the safety of long-term abatacept use is not yet available.

Since abatacept abrogates a key pathway leading to T cell activation, the drug is under clinical investigation in a number of other T cell-mediated inflammatory diseases, including psoriasis and systemic lupus erythematosus. In a Phase I study in psoriasis vulgaris, 46% of 43 patients receiving open-labeled CTLA4Ig had sustained disease improvement of 50% or greater, and clinical response was associated with a reduction in the number of T cells infiltrating psoriatic lesional skin [52]. CTLA4Ig has also produced disease inhibition in murine models of lupus and is currently undergoing clinical evaluation in systemic lupus erythematosus [53].

1.4.5.2 CTLA4 Targeting

Cytotoxic T lymphocyte antigen-4 (CTLA4) is a negative regulator of T cell activity that counteracts T cell activation and proliferation by its co-stimulatory counterpart CD28. Due to its role in T cell deactivation, CTLA4 has been implicated as a molecular target for cancer therapy. Through inhibition of a critical negative regulator of the immune cascade, anti-CTLA4 antibodies exert their antitumor effect by amplifying the innate immune response to cancer.

Two humanized CTLA4-targeting monoclonal antibodies, MDX-010 and CP-675206, are currently under investigation in Phase I and II clinical trials. Maximum doses of 3.0 mg/kg for MDX-010 [54] and 15 mg/kg for CP-675,206 [55] have been established in Phase I trials. Most studies have enrolled patients with metastatic melanoma or renal carcinoma, among whom anti-CTLA4 therapy produced objective tumor response rates of 7–15% [56]. In a study of 56 patients with progressive stage IV melanoma, coadministration of peptide vaccination did not appear to enhance the antitumor effect of MDX-010 [57]. Phase III testing of MDX-010 in melanoma, comparing the efficacy of antibody in combination with melanoma peptides to each agent as monotherapy, is underway.
Adverse immune reactions are commonly experienced by patients taking CTLA4 antibodies, including some serious (grade 3–4) reactions. Cutaneous and gastrointestinal autoimmune toxicities are most frequent, and the majority of treatment-induced autoimmune events resolve with cessation of anti-CTLA4 therapy and administration of high-dose steroids [56]. A positive correlation between serious autoimmune toxicity and clinical response to treatment has been reported [57].

### 1.4.5.3 IL-12/23 p40 Targeting

IL-12 and IL-23 play an essential role in the induction and maintenance of the T helper (Th) 1 immune response and are implicated in the pathogenesis of psoriasis, a Th1-mediated inflammatory disease. Monoclonal antibodies targeted to p40, a common subunit of IL-12 and IL-23, inhibit the interactions of both interleukins with cell surface receptors and thus abrogate key proinflammatory signals. Treatment of psoriasis patients with anti-p40 antibody leads to downregulation of IL-12 and IL-23 as well as downstream Th1 cytokines [58].

The safety and efficacy of anti-p40 antibody as therapy for psoriasis is currently under clinical investigation. In two Phase I trials of the antibody in plaque psoriasis, in which the drug was administered to a total of 35 patients with plaque psoriasis, no serious adverse events were observed, and a 75% or greater reduction in PASI was achieved by a majority of subjects [59], [60]. In a Phase II trial of a fully humanized monoclonal anti-IL-12/23 antibody (CNTO 1275) [61], at least 75% PASI improvement at 12 weeks was seen, in 52% of patients who received a single 45 mg dose of the antibody, in 59% of patients who received 90 mg, in 67% of those who received four weekly 45 mg doses, and in 81% of those who received four weekly 90 mg doses. Serious adverse events occurred in 4% of patients receiving the antibody, compared with 1% of those receiving placebo. Further trials will define optimal dosing regimens of anti-p40 antibody for the treatment of psoriasis.

### 1.4.5.4 Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIg) is a solution consisting of immunoglobulins extracted from the pooled plasma of several thousand blood donors, with the final product representing the entire range of antibodies found in normal human serum. IVIg was initially developed as replacement therapy for patients with primary or acquired humoral immunodeficiencies, but over the past decade, high-dose IVIg has increasingly been used to treat immune-mediated inflammatory disease. The therapeutic action of IVIg in autoimmune disorders is mechanistically complex and involves an array of immunomodulatory functions, many of which are not completely understood.

IVIg has been used to treat inflammatory dermatoses as well as multi-system diseases with cutaneous involvement, usually after the failure of first-line treatment modalities. While IVIg is officially approved for a wide range of clinical indications, about half of overall IVIg use is off-label [62]. The most common off-label uses of IVIg in dermatology are for treatment of the autoimmune bullous diseases and toxic epidermal necrolysis (TEN). Disease remission was observed in 81% of reported cases of IVIg-treated pemphigus vulgaris and 70% of bullous pemphigoid cases; success of IVIg therapy has also been reported in pemphigus foliaceus, cicatricial pemphigoid, and epidermolysis bullosa acquisita [63]. In a retrospective analysis of 48 cases of TEN, IVIg treatment (mean total dose of 2.7 g/kg) was associated with rapid cessation of epidermal detachment in 90%, and survival in 88%, of patients [64].

Success of IVIg therapy has been reported in a number of other dermatologic and rheumatic diseases with cutaneous manifestations, including dermatomyositis [65], systemic and cutaneous lupus erythematosus [66], AD, chronic urticaria, scleromyxedema, and pyoderma gangrenosum [67]. IVIg is particularly useful for the treatment of Kawasaki disease, in which it is currently the primary standard of care [58].

IVIg therapy is generally well tolerated. The most common adverse events are minor infusion reactions such as headache, nausea, and low-grade fever, and slower rate of infusion is associated with improved tolerability. Adverse reactions are experienced by about 10% of patients who receive IVIg [58] and are substantially less common in patients receiving IVIg for autoimmune diseases than in immunodeficient patients. Rarely, high-dose IVIg therapy can lead to acute renal failure and cardiovascular toxicity [68].
1.4.6 Prophylaxis and Precautions

Immune response modifying therapies are useful for the treatment of many dermatologic diseases. Rituximab and MMF have been used to reduce the number of B cells, by leading to cell death or the inhibition of proliferative activity. Drugs that target T cell-mediated immune cascades include alefacept, efalizumab, and the calcineurin inhibitors, cyclosporin and tacrolimus. Recently, the TNF-α antagonists, infliximab, etanercept, and adalimumab, have entered the dermatology repertoire, providing effective new treatment options for the management of numerous autoimmune diseases. Other immune pathway antagonists include abatacept and anti-CTLA4 antibodies, which act as negative and positive regulators of T cell activity, respectively. Treatment with IVIg has also shown efficacy in the treatment of some dermatologic conditions. These immunomodulatory drugs employ a variety of mechanisms, leading either to the suppression or amplification of specific immune responses, to treat immune-mediated diseases.

While these drugs may effectively target pathologic immune functioning, they also exert nonspecific effects that can potentially lead to serious problems. In order to minimize risks, careful selection and follow-up of patients is important. Blood count and differential should be monitored in patients receiving long courses of immune-modifying medications. Any immunosuppressive therapy confers an increased risk of infection, and the development of an infection may require interruption or cessation of therapy. Of concern, reactivation of latent tuberculosis has been reported in patients receiving abatacept and the TNF-α antagonists. Therefore, patients should be screened for tuberculosis with a purified protein derivative (PPD) skin test prior to undergoing therapy with one of these agents.

Additionally, many immunomodulatory therapies are associated with an increased risk of malignancy in the long-term. Use of the TNF-α targeting agents [69], cyclosporin [70], and abatacept [50] is associated with an elevated risk of lymphoma, although causative relationships have not been established. A slightly increased incidence of cutaneous malignancy has been described in patients receiving mycophenolate mofetil [71], and long-term abatacept use may increase the risk of lung cancer [50]. Due to a concern about a potentially increased risk of UV-induced carcinogenesis, patients using topical tacrolimus are advised to avoid excessive UV exposure. Long-term safety profiles for many of these drugs, which have only recently become clinical mainstays, are not yet established. Continued clinical investigation and the emergence of longitudinal data will further elucidate the safety of immune-modifying agents for the management of dermatologic diseases.

References


1.5.1 Principles of Genetics

The word “genetics” (from the Greek genno = give birth) was first used to describe the study of inheritance and the science underlying the variation in progeny. It was coined by the British scientist William Bateson in 1905 and was first used in this context at the Third International Conference on Plant Hybridization in 1906 [1]. The realization that inherited traits could be studied arose from Bateson’s relationships with clinicians interested in inherited disorders. In particular, his collaboration with Archibald Garrod regarding the recessive inheritance of alkaptonuria was early evidence of coordination between physicians and genetic researchers.

In the past century, research discoveries in this field have grown exponentially, especially over the past two decades. The sensitivity and specificity of diagnosing inherited disorders have drastically improved due to the advent of new diagnostic techniques such as the polymerase chain reaction (PCR), real time PCR, in situ hybridization, and fluorescent in situ hybridization (FISH) [2–4]. This capability has been further enhanced by tools derived from the Human Genome Project, which was a major advance in the study of heritable diseases.

Over the years, researchers have succeeded in identifying specific mutations in hundreds of genes that are responsible for various heritable diseases. Many of these conditions have involvement in skin, hair, or nails [5], thereby providing some explanations for the cutaneous findings documented by clinicians [6]. Moreover, the skin is the largest and the most accessible organ in the human body and has accordingly received extensive attention. The skin is not only a convenient target for gene therapy of cutaneous diseases, but can also be exploited in targeting therapies for other affected tissues. As remarkable as the achievements in genetic research have been, the access to patients by physicians places them to a unique position as it offers them direct access to the genetic basis of diseases—patient’s DNA. This relationship affords physicians the opportunity to understand the basic concepts of genetics using new molecular diagnostic techniques.

Furthermore, the vast flow of new discoveries by researchers all over the world on almost a daily basis implies that physicians alone would be overwhelmed by this mass of newly accumulating knowledge. Thus, as Bateson and Garrod have exemplified, a good collaboration between clinicians and researchers in the field of medicine is a powerful tool for further discovery of new aspects of human diseases and for developing novel methods to treat them.

A.M. Christiano
Department of Dermatology, Columbia University, New York Presbyterian Hospital, 161 Fort Washington Avenue, 12th Floor, New York, NY 10032, USA
e-mail: amcle5@columbia.edu
1.5.2 Basics of Genetics

In the cell, most genetic information is stored in the nucleus and encoded by nuclear DNA, which is packed into distinct units called chromosomes (from the Greek: χρωμόσωμα = colored and σώμα = body). The human genome consists of 23 pairs of these chromosomes, including 22 pairs of autosomes and 1 pair of sex chromosome (XX for female, XY for male), denoting the karyotype of an individual. Each pair of chromosomes is composed of two homologous chromatids. In the quiescent cell, chromosomes are comprised of euchromatin and heterochromatin. These correspond to uncompacted actively transcribed DNA and compacted untranscribed DNA, respectively. Half of the chromosomes are inherited from the father and the other half from the mother. Sex cells, or gametes, are different from the diploid somatic cells, as they contain only 23 uniparental chromosomes and are described as haploid. The process of fertilization involves interaction of one paternal and one maternal gamete and results in the formation of a zygote. The zygote contains 23 pairs of chromosomes (diploid), where half of each pair belong to the male and the other half to the female parent. In the dividing cell, the chromosomes can be easily visualized under the microscope. There are two kinds of cell divisions: mitosis, the division of germ cells, and meiosis, the division of germ cells.

During cell division, homologous somatic chromosomes and the pair of sex chromosomes (XX or XY) become attached to each other and to the mitotic spindle by means of the centromere, the site of attachment of the two homologous chromosomes. The centromere divides each chromosome into two arms: the short arm, p, and the long arm, q. According to the chromosome classification, the chromosome is metacentric if the centromere location is close to the midpoint of the chromosome (e.g., chromosome 1) and both chromosome arms (p and q) are approximately of the same length. Submetacentric chromosomes have centromeres displaced toward one end (e.g., chromosome 4), whereas acrocentric chromosomes have centromeres displaced toward the tip of one end. In acrocentric chromosomes, the p arm carries very little genetic information.

The telomere is a region of highly repetitive DNA at the distal end of the chromosome that is not believed to carry crucial genetic information, but is present to prevent degradation of coding and regulatory regions during DNA replication. The length of the telomeres tends to decrease each time the genome is replicated in preparation for cell division; the loss of telomeres has been proposed as an explanation for the loss of the ability to divide, and by extension, for the aging process in organisms [7].

The specific location of a DNA sequence on a particular chromosome is known as a locus. This DNA sequence specifies the amino acids that comprise a protein, generated by the expression of a given gene. Every individual has two copies of each chromosome and these loci can be identical or different. These alternative forms of genetic information at a particular locus are called alleles. Therefore, every individual has two sets of loci (alleles), one is paternal and the other is maternal. If two homologous loci are identical they are called homozygous; whereas if they are different, they are known as heterozygous.

Not all differences in alleles at a specific locus are attributable to mutations. Some are known as polymorphisms, which are common normal variants at a specific locus that do not result in disease phenotype. Furthermore, these polymorphisms can be used as genetic markers for a particular gene, when this polymorphism and the gene are in close proximity.

The genetic constitution of a single locus defines the individual genotype. In turn, the genotype is responsible for the phenotype, the outward physical manifestation of one or several traits via the interaction of the gene of interest with other genes and/or environmental factors.

1.5.3 Overview of Genetic Disease

The mechanistic understanding brought by recent advancements in molecular genetics has refined some classical genetic principles. Despite these developments, many of them remain intact, particularly the original premises of Gregor Mendel. He initially described the inheritance pattern of genetic traits in pea plants and their mathematical correlations in his paper “Versuche ueber Pflanzenhybriden” (“Experiments in plant hybridization”) in 1865. To this day, single-gene traits are often referred to as Mendelian, because they segregate within families...
1.5 Basic Principles of Genetics and Gene Therapy

and transmit fixed proportion of characteristics to their offspring.

While some genetic diseases are caused by a mutation in one gene (Mendelian or monogenic), others are the result of mutations in two or more genes (polygenic); they may also be the result of a complex interaction of environmental and genetic factors (multifactorial diseases) [8]. After identifying mutations in many monogenic diseases, the attention in dermatology and other fields has gradually shifted to determining the etiology of polygenic and multifactorial disorders such as psoriasis and alopecia areata [9, 10].

1.5.4 Overview of Mendelian Genetics

Since a diagnosis based on only clinical findings can sometimes be misleading, it is important for clinicians to supply maximal information in order to establish the correct pattern of transmission. A detailed family history including information about the phenotype and the specific relationships between each individual of that particular family should be obtained in order to summarize all details in the form of a pedigree.

The patterns demonstrated by pedigrees for a single gene disorder allow the mode of inheritance of a disease to be determined. The genes responsible for monogenic traits can be located on autosomes (autosomal) or X-chromosome (X-linked). If only one allele of the genome gives rise to a disease phenotype, it is called dominant; if two copies are required for the development of a disease phenotype, it is considered recessive. The majority of genetic diseases vary in the severity of their phenotypic expression, with some individuals showing more profound disease than others. This can be due to environmental influences, genetic background, or as a consequence of locus or allelic heterogeneity. In the case of locus heterogeneity (Table 1.5.1), the same phenotype can be the result of mutations in different genes. In dermatology, there are multiple examples of such diseases. For instance, Naxos disease (MIM601214) can be caused by mutations in either the desmoplakin or plakoglobin gene [11, 12]. Palmoplantar epidermolysis keratoderma (MIM144200), first described by Voerner 1901 [13], can be caused by mutations in the keratin 1 (chromosome 12; MIM139350) or keratin 9 gene (chromosome 17; MIM607606 [14]), whereas the nonepidermolytic form (MIM600962), described by Thost 1880 and by Unna 1883 [15, 16], arises from the mutations in either keratin 1 (chromosome 12; MIM139350) [17] or keratin 16 (chromosome 17; MIM148067) [18]. Mutations of the KRT1 and KRT9 gene that are associated with the epidermolytic form of PPK affect the central regions of the protein (important for its assembly and stability), whereas mutations in the KRT1 gene associated with the nonepidermolytic form involve the amino-terminal variable end region [19]. The palmoplantar keratoderma form of Unna-Thost disease is clinically identical to the localized epidermolytic hyperkeratosis of Voerner. They can be only distinguished historically in the presence (Voerner) or absence (Unna-Thost) of epidermolysis [20]. Monilethrix (MIM158000) is another example of locus heterogeneity. This disorder is characterized by beaded or moniliform hair and can be caused by mutations in the hair keratin genes KRTHB1 (MIM 602153), KRTHB3 (MIM 602765) or KRTHB6 (MIM 601928), when inherited in an autosomal dominant fashion [21, 22]. On the other hand, this disease can be inherited in an autosomal recessive fashion as a consequence of a mutation in the desmoglein 4 gene (MIM 607892) [23–25].

Allelic heterogeneity (Table 1.5.2) occurs when different mutations in the same gene result in a variety of phenotypes. For example, various mutations in the collagen VII (MIM120120) gene cause different types of dystrophic epidermolysis bullosa (EB). The Pasini type of generalized dystrophic EB (MIM 131750) with albopapuloid lesions is due to dominant inheritance and the Hallopeau–Siemens EB type (MIM226600) with pseudosyndactyly and mucous membrane involvement results when inherited recessively.

Hay-Wells syndrome, also known as AEC syndrome (ankyloblepharon ectodermal dysplasia and cleft lip/palate) (MIM106260) is a rare autosomal dominant disorder characterized by congenital ectodermal dysplasia, including alopecia, scalp infections, dystrophic nails, hypodontia, ankyloblepharon, and cleft lip and/or cleft palate. It is caused by mutations in the p63 gene; whereas other mutations in p63 can cause EEC syndrome (ectrodactyly-ectodermal dysplasia-cleft lip/palate) (MIM604292) [26, 27], with a different phenotype.
Table 1.5.1: Examples of genetic or locus heterogeneity in genodermatoses

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene symbol</th>
<th>Gene or gene product</th>
<th>MIM number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidermolytic hyperkeratosis</td>
<td><strong>KRT1</strong></td>
<td>Keratin 1</td>
<td>139350</td>
</tr>
<tr>
<td></td>
<td><strong>KRT10</strong></td>
<td>Keratin 10</td>
<td>148080</td>
</tr>
<tr>
<td>Erythrokeratodermatitis variabilis (Mendes da Costa)</td>
<td><strong>Cx31</strong></td>
<td>Connexin 31</td>
<td>603324</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Connexin 30.3</td>
<td>148210</td>
</tr>
<tr>
<td>Lamellar ichthyosis</td>
<td><strong>TGM1</strong></td>
<td>Transglutaminase 1</td>
<td>190195</td>
</tr>
<tr>
<td></td>
<td><strong>ICR2B</strong></td>
<td>Arachidonate Lipoxygenase 3</td>
<td>607206</td>
</tr>
<tr>
<td></td>
<td><strong>LI2</strong></td>
<td>Arachidonate 12- Lipoxygenase, R Type E 3</td>
<td>603741</td>
</tr>
<tr>
<td>Nonbullous congenital ichthyosiform erythroderma</td>
<td><strong>TGM1</strong></td>
<td>Transglutaminase 1</td>
<td>190195</td>
</tr>
<tr>
<td></td>
<td><strong>ALOX12B</strong></td>
<td>Arachidonate Lipoxygenase 3</td>
<td>607206</td>
</tr>
<tr>
<td>Palmoplantar keratoderma, epidermolytic (Voerner)</td>
<td>(<strong>KRT1</strong></td>
<td>Keratin 1</td>
<td>139350</td>
</tr>
<tr>
<td></td>
<td><strong>KRT9</strong></td>
<td>Keratin 9</td>
<td>144200</td>
</tr>
<tr>
<td>Palmoplantar keratoderma, nonepidermolytic (Unna-Thost)</td>
<td>(<strong>KRT1</strong></td>
<td>Keratin 1</td>
<td>600962</td>
</tr>
<tr>
<td></td>
<td><strong>KRT16</strong></td>
<td>Keratin 16</td>
<td>148067</td>
</tr>
<tr>
<td>Palmoplantar keratoderma with deafness</td>
<td><strong>MTTS1</strong></td>
<td>Mitochondrial tRNA-serine 1</td>
<td>148350, 590080</td>
</tr>
<tr>
<td></td>
<td><strong>CX26, GJB2</strong></td>
<td>Connexin 26</td>
<td>148350, 121011</td>
</tr>
<tr>
<td>Striate palmoplantar keratoderma (Bruenauer-Fuhs-Siemens)</td>
<td><strong>DSP</strong></td>
<td>Desmoplakin</td>
<td>125647</td>
</tr>
<tr>
<td></td>
<td><strong>DSG1</strong></td>
<td>Desmoglein 1</td>
<td>125670</td>
</tr>
<tr>
<td>Naxos disease</td>
<td><strong>JUP</strong></td>
<td>Plakoglobin</td>
<td>173325</td>
</tr>
<tr>
<td></td>
<td><strong>DSP</strong></td>
<td>Desmoplakin</td>
<td>125647</td>
</tr>
<tr>
<td>Monilethrix</td>
<td><strong>KRTHB1</strong></td>
<td>Hair keratin, basic 1</td>
<td>602153</td>
</tr>
<tr>
<td></td>
<td><strong>KRTHB3</strong></td>
<td>Hair keratin, basic 3</td>
<td>602765</td>
</tr>
<tr>
<td></td>
<td><strong>KRTHB6</strong></td>
<td>Hair keratin, basic 6</td>
<td>601928</td>
</tr>
<tr>
<td>White sponge nevus</td>
<td><strong>KRT4</strong></td>
<td>Keratin 4</td>
<td>123940</td>
</tr>
<tr>
<td></td>
<td><strong>KRT13</strong></td>
<td>Keratin 13</td>
<td>148065</td>
</tr>
<tr>
<td>EBS Weber-Cockayne variant</td>
<td><strong>KRT5</strong></td>
<td>Keratin 5</td>
<td>148040</td>
</tr>
<tr>
<td></td>
<td><strong>KRT14</strong></td>
<td>Keratin 14</td>
<td>148066</td>
</tr>
<tr>
<td>EBS Dowling-Meara variant</td>
<td><strong>KRT5</strong></td>
<td>Keratin 5</td>
<td>148040</td>
</tr>
<tr>
<td></td>
<td><strong>KRT14</strong></td>
<td>Keratin 14</td>
<td>148066</td>
</tr>
<tr>
<td>EBS Koebner</td>
<td><strong>KRT5</strong></td>
<td>Keratin 5</td>
<td>148040</td>
</tr>
<tr>
<td></td>
<td><strong>KRT14</strong></td>
<td>Keratin 14</td>
<td>148066</td>
</tr>
<tr>
<td>JEB Herlitz</td>
<td><strong>LAMC2</strong></td>
<td>Laminin-5 polypeptide subunit α2</td>
<td>150292</td>
</tr>
<tr>
<td></td>
<td><strong>LAMB3</strong></td>
<td>Laminin-5 polypeptide subunit β3</td>
<td>150310</td>
</tr>
<tr>
<td></td>
<td><strong>LAMA3</strong></td>
<td>Laminin-5 polypeptide subunit α3</td>
<td>600805</td>
</tr>
<tr>
<td>JEB Non-Herlitz</td>
<td><strong>COL17A1</strong></td>
<td>Collagen XVII</td>
<td>113811</td>
</tr>
<tr>
<td></td>
<td><strong>ITGB4</strong></td>
<td>β4-Integrin</td>
<td>147557</td>
</tr>
<tr>
<td></td>
<td><strong>LAMC2</strong></td>
<td>Laminin-5 polypeptide subunit α2</td>
<td>150292</td>
</tr>
<tr>
<td></td>
<td><strong>LAM3B</strong></td>
<td>Laminin-5 polypeptide subunit β3</td>
<td>150310</td>
</tr>
<tr>
<td></td>
<td><strong>LAMA3</strong></td>
<td>Laminin-5 polypeptide subunit α3</td>
<td>600805</td>
</tr>
<tr>
<td>EEC syndrome</td>
<td><strong>EEC1</strong></td>
<td>p63</td>
<td>129900</td>
</tr>
<tr>
<td></td>
<td><strong>EEC2</strong></td>
<td></td>
<td>602077</td>
</tr>
<tr>
<td></td>
<td><strong>TP63</strong></td>
<td></td>
<td>603273</td>
</tr>
<tr>
<td>Hypohidrotic ED</td>
<td><strong>EDAR</strong></td>
<td>Ectodysplasin receptor</td>
<td>604095</td>
</tr>
<tr>
<td></td>
<td><strong>EDARADD</strong></td>
<td>EDAR-associated death domain</td>
<td>606603</td>
</tr>
<tr>
<td>Griscelli syndrome</td>
<td><strong>MYO5A</strong></td>
<td>Myosin a</td>
<td>160777</td>
</tr>
<tr>
<td></td>
<td><strong>RAB27A</strong></td>
<td>RAS-associated protein</td>
<td>603868</td>
</tr>
</tbody>
</table>
### Table 1.5.1  (continued)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene symbol</th>
<th>Gene or gene product</th>
<th>MIM number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hermansky-Pudlak syndrome</td>
<td>HPS1</td>
<td>Transmembrane protein</td>
<td>604982</td>
</tr>
<tr>
<td></td>
<td>HPS2</td>
<td>Adaptor-related protein complex 3</td>
<td>603401</td>
</tr>
<tr>
<td></td>
<td>HPS3</td>
<td>HPS3</td>
<td>606118</td>
</tr>
<tr>
<td></td>
<td>HPS4</td>
<td>HPS4</td>
<td>606682</td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td>PAH</td>
<td>Phenylalanine hydroxylase</td>
<td>261600</td>
</tr>
<tr>
<td></td>
<td>DHPR</td>
<td>Dihydropteridine reductase</td>
<td>261630</td>
</tr>
<tr>
<td></td>
<td>PTS</td>
<td>6-Pyruvoylta-hydroxylase</td>
<td>261640</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>TSC1</td>
<td>Hamartin</td>
<td>605284</td>
</tr>
<tr>
<td></td>
<td>TSC2</td>
<td>Tuberin</td>
<td>191092</td>
</tr>
<tr>
<td>Epidermodyplasia verruciformis</td>
<td>EV1</td>
<td>EVER1 (Integral membrane protein of the endoplasmic reticulum 1)</td>
<td>605828</td>
</tr>
<tr>
<td></td>
<td>EV2</td>
<td>EVER2</td>
<td>605829</td>
</tr>
<tr>
<td>Muir-Torre-syndrome</td>
<td>hMSH2</td>
<td>MutS, E.coli, homolog</td>
<td>609309</td>
</tr>
<tr>
<td></td>
<td>hMLH1</td>
<td>MutL, E.coli, homolog</td>
<td>120436</td>
</tr>
<tr>
<td>Cockayne syndrome</td>
<td>ERCC6 or CSB</td>
<td>Excision-repair coss-complementing, group 6</td>
<td>609413</td>
</tr>
<tr>
<td></td>
<td>ERCC8 or CSA</td>
<td>Excision-repair coss-complementing, group 8</td>
<td>609412</td>
</tr>
<tr>
<td>Noonan syndrome</td>
<td>PTPN11</td>
<td>Nonreceptor protein tyrosine phosphatase SHP2</td>
<td>176876</td>
</tr>
<tr>
<td></td>
<td>SOS1</td>
<td>Son of sevenless, drosophila, homolog 1</td>
<td>182530</td>
</tr>
<tr>
<td></td>
<td>KRAS</td>
<td>V-Ki-Ras2 Kirsten rat sarcoma viral oncogene homolog</td>
<td>190070</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>Neurofibromin gene</td>
<td>162200</td>
</tr>
<tr>
<td>Ommen syndrome</td>
<td>RAG1</td>
<td>Rag-1</td>
<td>179615</td>
</tr>
<tr>
<td></td>
<td>RAG2</td>
<td>Rag-2</td>
<td>179616</td>
</tr>
</tbody>
</table>

### Table 1.5.2  Examples of allelic heterogeneity in genodermatoses

<table>
<thead>
<tr>
<th>Gene</th>
<th>MIM</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>GJB3</td>
<td>603324</td>
<td>Erythrokeratoderma variabilis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AD nonsyndromic sensorineural deafness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AR nonsyndromic hearing loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AD deafness with peripheral neuropathy</td>
</tr>
<tr>
<td>Desmoplakin</td>
<td>125647</td>
<td>Striate palmoplantar keratoderma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dilated cardiomyopathy with woolly hair and keratoderma (Naxos)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epidermolyisis bullosa, lethal acantholytic</td>
</tr>
<tr>
<td>Plectin</td>
<td>601282</td>
<td>EBS with limb-girdle muscular dystrophy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EBS Ogna type</td>
</tr>
<tr>
<td>KRT1</td>
<td>139350</td>
<td>Bullous congenital ichthyosiform erythroderma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epidermolytic palmoplantar keratoderma (Voerner)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonepidermolytic palmoplantar keratoderma (Unna-Thost)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ichthyosis hystrix (Curth-Macklin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epidermolytic hyperkeratosis of BrocQ</td>
</tr>
<tr>
<td>TGM1</td>
<td>190195</td>
<td>Lamellar Ichthyosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonbullous congenital ichthyosiform erythroderma</td>
</tr>
<tr>
<td>COL7A1</td>
<td>120120</td>
<td>Recessive dystrophic EB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dominant dystrophic EB</td>
</tr>
</tbody>
</table>
1.5.5 Autosomal Dominant Inheritance

Autosomal dominant mutations (Fig. 1.5.1a) are relatively rare in populations. In general, the typical pattern is that heterozygous affected individuals mate with homozygous normal individuals. Because anyone who carries the disease-causing gene is affected, the disease is typically observed in all generations. It affects both males and females equally, with a recurrence risk of 50%, in offspring of affected individuals. Several skin diseases are inherited in an autosomal dominant manner: dystrophic EB with mutations in the COL7A1 gene (MIM120120), EB simplex with mutations in keratin 5 (MIM148040) or keratin 14 gene (MIM148066), the epidermolytic hyperkeratosis with mutations in keratin 10 gene (MIM148080), Darier’s disease (MIM108740) also known as keratosis follicularis, which is characterized by warty papules and plaques in seborrheic areas with mutations in the ATP2A2 gene [28], Neurofibromatosis (MIM162200) with NF1 mutation or even monilethrix (MIM158000) [29]. Individuals with two mutant alleles develop more severe phenotype than those who are heterozygous for the mutation containing allele. Examples include dystrophic EB [30], monilethrix, and mutation in the keratin14 gene. There are a number of exceptions to this rule due to incomplete penetrance, variable expression, or de novo mutations, which will be discussed later (see below).

1.5.6 Autosomal Recessive Inheritance

Autosomal recessive mutations are clinically expressed only in the homozygous state (Fig. 1.5.1a, b). The offspring must inherit a copy of the disease-causing allele from each parent. The disease affects both sexes equally as the mutation is located on an autosomal chromosome. There is no transmission from generation to generation; therefore the proband may be the only affected family member. Sometimes relatives can be also affected, especially in large inbred or consanguineous families. Homozygous recessive offspring most commonly result from the union of two heterozygous parents. Compound heterozygosity may also result in a recessive phenotype if two different mutations occur in the same gene. The recurrence risk in offspring is thus 25%. There are a number of examples of recessive inheritance. One example is Naxos disease (MIM601214) [31]. It appears with palmoplantar keratoderma and other ectodermal features such as cardiac disorders [12]. Another example of autosomal recessive inheritance is lamellar ichthyosis (MIM242300), caused by mutations in the gene...
forkeratinocyte transglutaminase (TGM1; MIM190195), which is located on chromosome 14 [32]. Netherton syndrome (MIM256500), which is caused by mutations in the SPINK5 gene (MIM605010), encoding the serine protease inhibitor LEKTI is another one [33]. The latest was first reported by Netherton (1958) showing the typical “bamboo hair” (trichorrhexis nodosa), congenital ichthyosiform erythroderma and atopic diathesis [34].

Recessive disorders are not common, as they require two heterozygous carriers to mate. When generating a pedigree, it is important to consider the possibility of consanguinity, even if denied by the parents, and especially if they come from small isolated geographic areas. If one of the ancestors was a carrier for a particular mutation, the frequency of this mutation could be elevated in the population. This effect is known as a founder effect. For example, it is seen in the French Canadian community, where mutations in the connexin 30 gene (GJB6) (MIM604418) are highly prevalent [35]. This mutation results in hidrotic ectodermal dysplasia (HED, Clouston syndrome MIM 129500), a disorder that causes defects in nails and hair and accompanied by palmoplantar keratoderma [36].

1.5.7 X-Linked Dominant Inheritance

Focal dermal hypoplasia, first described by Goltz in 1962 (Goltz Syndrome) (MIM175200) [37] and incontinentia pigmenti (Bloch-Sulzberger Syndrome; MIM 308300) [13, 38] are two examples of the relatively few diseases classified as X-linked dominant (Fig. 1.5.1d). The pedigree of an X-linked dominant disorder does not show male-to-male transmission, but as in autosomal dominant inheritance, the disease phenotype is evident in multiple generations.

The recurrence risk also depends on the transmitting parent. An affected hemizygous male should theoretically transmit the trait to all of his daughters, but not to his sons. If the mother is affected, her sons and daughters each have approximately a 50% chance of inheriting the mutant gene. The mutations in focal dermal hypoplasia and incontinentia pigmenti are manifested only in females because affected males do not have a second X chromosome with a normal allele and are usually lethal in utero. The heterozygous female with incontinentia pigmenti caused by mutations in the NEMO gene (nuclear factor kB essential modulator) on Xq28, typically shows vesicular lesions following the lines of Blaschko [39]. As an X-linked skin disorder, Lyonization usually gives rise to a mosaic pattern, manifested by the appearance of the lines of Blaschko [40].

1.5.8 X-Linked Recessive Inheritance

Normally males inherit an X chromosome from their mother and a Y chromosome from their father, whereas females inherit one X chromosome from each of their parents (Fig. 1.5.1c). The X chromosome carries more than a hundred genes and the Y chromosome carries approximately 30 genes. Therefore, there must be a mechanism that equalizes the levels of proteins associated with the X chromosome in both males and females. This mechanism, known as Lyonization named after the Lyon hypothesis, in honor of Dr. Mary Lyon who proposed this principle, randomly inactivates one of the two female X-chromosomes in each cell during the early embryogenesis at the stage of the morula, 3 days after fertilization. As the inactivation is random, it may cause mosaicism; in other words, the consequences of a gene mutation are present only in a percentage of cells. Therefore, one of the characteristic features of X-linked recessive traits is that female carriers are often asymptomatic, even though some express the condition with lesser severity. These diseases do not have male-to-male transmission because a father passes the Y chromosome to his sons, not the X chromosome. Typical examples of X-linked recessive inheritance are Menke’s syndrome (MIM309400) [41], also called “Kinky hair disease”, caused by mutations in the copper transporter ATP7A [42] and X-linked recessive ichthyosis (MIM308100) caused by mutations in the steroid sulfatase gene [43]. Among all genetic disorders, X-linked ichthyosis shows one of the highest ratios of chromosomal deletions; complete deletion has been found in up to 90% of patients [44]. Another example is the X-linked hypohidrotic ectodermal dysplasia (HED) (MIM305100), which is caused by mutation in the gene encoding ectodysplasin-A (EDA; MIM 300451). In this inherited form of HED, males are usually affected more severely. Females instead show variable severity, ranging from mild to severe defects in the morphogenesis of ectodermal structures, such as hair, skin, nails, and teeth [45].

The gene DKC1, located in the Xq28 region, undulates X-linked recessive dyskeratosis congenita (DKC; 305000), also known as Zinsser–Cole–Engman
syndrome [46]. The disease is characterized by the early manifestation of reticulate skin pigmentation, nail dystrophy, and mucosal leukoplakia. Only males are affected in a pattern consistent with X-linked recessive inheritance [47]. Recessive ectodermal dysplasia (ED) causes a generalized, but not lethal skin defect in males. However, the affected females, who carry the X-linked dominant inherited disease show highly variable pathology of the skin, hair, nails, teeth, eyes, and central nervous system [45, 48].

1.5.9 Incomplete Penetrance, Delayed Onset Diseases, Variable Expression, De Novo Mutations, Segmental and Germline Mosaicism

1.5.9.1 Incomplete Penetrance and Delayed Onset Disease

Incomplete penetrance in a pedigree is defined by the presence of individuals who have the disease genotype, but do not necessarily manifest the phenotype. Incomplete penetrance is distinguished from variable expression, which indicates that the penetrant gene has variation in phenotypic expression of the same genotype. Both recessive and dominant diseases can demonstrate incomplete penetrance. For example, multiple cutaneous and uterine leiomyomatosis (MIM150800), an autosomal dominant disorder caused by mutations in the gene encoding fumarate hydratase [49, 50], may manifest in alternate generations of a family, though all members of the family carry the same genotype. Phenotypically, however, they appear normal and the trait gives the impression as if a generation was skipped.

Another form of incomplete penetrance is the delayed age of onset disease. Although individuals carry the mutation, they do not show the typical phenotype until a certain age, which can lead to a false interpretation. Darier’s Disease (MIM124200) also known as keratosis follicularis, is caused by a mutation in the ATP2A2 gene. Hailey-Hailey Disease (MIM169600) [51, 52], also called familial benign chronic pemphigus, is due to a mutation in the ATP2C2 gene on chromosome 3q21-q24, encoding an adenosine triphosphate-powered calcium channel pump [52, 53]. These disorders are two typical examples of late onset diseases and are autosomal dominant traits. Seventy percent of Darier’s Disease patients manifest the disease phenotype between the ages of 6 and 20 years, with a peak onset during puberty, between 11 and 15 years [54]. Hailey-Hailey patients on the other hand, typically develop the initial symptoms and lesions during the second or third decade of life or may have further delayed disease onset in the fourth or fifth decade of life [55, 56].

1.5.9.2 Variable Expression

Disease severity may also vary among affected individuals. Due to allelic or locus heterogeneity, genetic background or environment influences, some individuals may be severely affected, whereas others may only have mild phenotypic expression. Peutz-Jeghers syndrome [57, 58] (MIM175200) is an autosomal trait demonstrating a high degree of penetrance and variable expressivity [59]. It is characterized by multiple lentigines, intestinal polyposis, and increased risk of carcinoma due to mutations in the STK11 gene.

Monilethrix (MIM158000), caused by a mutation in human hair keratin (HB1, HB6), is another example of variable expressivity. Abnormalities may be clinically subtle or not detectable at first glance, but upon careful examination of the body hair, some typical beaded hair shafts may be evident [60].

1.5.9.3 De Novo Mutations and Germline Mosaicism

In many genetic diseases, a large proportion of cases are caused by a new mutation transmitted from an unaffected parent to their newly affected offspring. Under these circumstances, there is no family history of the disease, and because the mutations occur spontaneously, the recurrence risk in future offspring of the same parents is very low. However, the rate of transmission from an affected individual to their offspring is the same as for any other autosomal trait (50%). The identification of de novo mutations, in particular, their
characterization and classification among other mutations, remains a difficult task and must be confirmed by genetic testing. De novo mutations have been identified in different types of EB, in the simplex form as well as in the dystrophic type [61, 62]. The incidence of NF1 (neurofibromatosis type 1, MIM162200) was given as approximately 1 in 3,500, and it was shown that about half of the cases are the result of new mutations. Therefore, it was shown that the mutation rate of the neurofibromatosis type 1 (NF1) gene is one of the highest in the human genome [63, 64]. In some cases, patients with an autosomal dominant disorder, e.g., EB simplex, will have an affected sibling even though neither of their parents is affected. This is due to gonadal or germline mosaicism- a postzygotic mutation that occurred in one parent’s genetic material during early embryonic development. Therefore, the mutation is present only in a portion of the father’s or the mother’s germ cells [62], as well as potentially some somatic cells, giving rise to different patterns of clinical involvement such as lines of Blaschko, a checkerboard pattern, a patchy pattern without midline separation, a phylloid pattern, and a lateralization pattern [65].

Genetic mosaicism has also been proposed to underlie the development of a rare subgroup of epidermal nevi, the linear epidermolytic hyperkeratosis, a localized malformation of the epidermis consisting of verrucoid scaly papules and plaques with alternating stripes of affected and unaffected skin that follow the lines of Blaschko. These nonrandom patterns may be caused by a postzygotic mutation in the keratin 1 and 10 gene during embryogenesis [66–68].

Segmental manifestation of disease is also observed in dermatology. In autosomal dominant skin diseases, two different types of segmental manifestations can be distinguished, reflecting different states of zygosity [69]. Type 1 shows a mild type of involvement, reflecting heterozygosity for a localized postzygotic mutation occurring at an early stage of embryogenesis in an otherwise normal embryo. This mutation leads to a localized population of heterozygous cells, resulting in a segmental disease. Type 1 mosaicism has explained epidermolytic epidermal nevi as mosaic variants of epidermolytic hyperkeratosis, segmental forms of Darier’s disease, neurofibromatosis type 1, tuberous sclerosis, and others [70]. In contrast, the second more severe type of segmental manifestation tends to occur in heterozygous embryos, which later develop a non-segmental, diffuse distribution of skin lesions. A postzygotic mutation occurring at an early developmental stage would result in loss of heterozygosity (LOH) and give rise to a mosaic population of cells, either homozygous or hemizygous for that allele [71, 72]. The corresponding phenotype would therefore be characterized by segmental lesions superimposed on a “classical” disease [73], as recently shown in Hailey-Hailey disease [69].

1.5.10 Chromosomal Abnormalities

Some genetic disorders may be the result of minute chromosomal aberrations [74]. Although chromosomal abnormalities can still be visualized on metaphase chromosomes under the microscope, several more advanced techniques that combine cytology with modern molecular technology have been recently discovered. FISH involves labeling a DNA segment with a fluorescent tag to create a probe, which is then hybridized to a homologous sequence of the patient’s chromosomes, and can then be visualized under a fluorescent microscope. An advantage of FISH is that the chromosomes do not have to be in metaphase, in order to accurately diagnose abnormalities. It also allows the identification of smaller changes in the chromosomes that are not detectable with conventional banding techniques.

Chromosome abnormalities occur in about 1: 150–250 newborns and thus are not considered rare. Approximately 65% of the spontaneous aborted fetuses examined for chromosomal defects had genetic abnormalities [75]. There are two major types of chromosomal abnormalities: numerical and structural. Numerical chromosomal abnormalities occur due to an excess or deficiency of one or few chromosomes (aneuploidy), or addition of at least one extra haploid set of chromosomes (polyploidy). Trisomies, the presence of an extra chromosome, are the most common numerical abnormalities, which are sometimes compatible with life. They occur as a result of nondisjunction (failure of chromosomal separation) during meiosis and their frequency increases with advanced maternal age. Trisomy 21, also known as Down syndrome, has an incidence of 1 in 800 live births and is a very common example of a trisomy with a classic phenotype, and thus, an easy clinical diagnosis (short nose, medial epicanthal fold, simian crease, etc.). Other
trisomies with characteristic features are Trisomy 8, Trisomy 18 (Edward’s) and Trisomy 13 (Pateau’s syndrome). Trisomy 16 appears with high frequency in studies of aborted fetuses but is not observed among newborns.

Aneuploidies involving the sex chromosomes are common and tend to have less severe consequences than autosomal aneuploidies. The two most common sex chromosome aneuploidies are Klinefelter syndrome (47, XXY) in which patients demonstrate tall stature, gynecomastia and varicose veins, and Turner syndromes (46, X0) with typical short stature and webbed neck. Over 95% of these fetuses are aborted spontaneously in the first trimester. Turner syndrome is the only monosomy compatible with life. Structural chromosomal abnormalities occur secondary to chromosome rearrangements, deletions of chromosomal material, or duplications. They can be balanced or unbalanced. Deletions of chromosome parts can result in the functional lack of one or a group of genes. For example, deletion of the short arm of chromosome 5 gives rise to cri du chat syndrome, which is characterized by a small stature, high-pitched, catlike cry and microcephaly. All of the advancements in genetic technology, FISH can be used to localize even submicroscopic deletions, as in X-linked ichthyosis (MIM308100). The majority of the males affected with this disorder have a complete deletion of the steroid sulfatase (STS) gene on chromosome Xp22.32 [76].

Hypertrichosis universalis congenita, Ambras type (MIM145701), is characterized by hypertrichosis that affects all body areas except for the regions on which normally no hair grows, such as palms, soles, mucosae, and dorsal terminal phalanges. Ambras syndrome is such a rare human syndrome that only a few cases have been reported in association with cytogenic anomalies [77, 78]. A detailed cytogenetic and molecular analysis showed a large deletion and an insertion of the q23-q24 region of chromosome 8 in one of these patients and a balanced pericentric inversion, inv (8)(p11.2q23.1), in the other [77, 79].

Another example is Williams-Beuren syndrome (WBS, MIM 194050). It is a contiguous gene syndrome caused by a microdeletion of the long arm of chromosome 7. The disorder was first described by Williams in individuals with growth retardation, unusual facial features, supravalvular aortic stenosis (SVAS), and mild mental retardation [80].

### 1.5.11 Polygenic Diseases

Atopic dermatitis (AD), also known as atopic eczema, commonly begins in infancy and early childhood. It is recognized as a strongly heritable, chronic, pruritic inflammatory skin condition [81, 82]. It affects 10–20% of children and 1–3% of adults [83] in industrialized countries, and shows a strong familial aggregation [84, 85]. Eighty percent cases of AD have elevations of the total serum IgE concentration. It is genetically complex, with multiple alleles at several loci thought to be involved in the pathogenesis. Candidate genes that might predispose to AD have been identified. The ADAM33 (a disintegrin and metalloprotease 33) on chromosome 20p was the first “asthma gene” to be discovered in 2002 [86]. IL-4 gene cluster of Th2 cytokines on chromosome 5 [87], mast-cell chymase gene on chromosome 14 [88], the high-affinity IgE receptor on chromosome 11 [89] or filagrin on chromosome 1 [90] are just some more examples [91].

Another example of multifactorial disease is psoriasis. It is a common inflammatory skin disease characterized by infiltration of inflammatory cells into the epidermis, abnormal keratinocyte proliferation/terminal differentiation, and dermal angiogenesis. Even though environmental factors, for instance, streptococcal infections and stress, affect the onset of the disease, family studies indicate a strong genetic component. To date, susceptibility loci for at least 10 genes have been recognized, including one for psoriatic arthritis (PSORS1-9, PSORAS1) [92, 93]. However, the exact genes and their functions, not have been definitely identified [94].

Alopecia areata (AA) (MIM104100) is a genetically determined, immune-mediated disorder of the hair follicle. The onset of the hair loss can be sudden without clinically visible inflammation with variety of clinical patterns. Owing to its prevalence in the population (2%) [95, 96], its concordance in twins (55%) [97], Gaussian distribution of severity [98], and the aggregation of affected individuals in families [99], AA fits into the paradigm of a complex or multifactorial genetic traits. Just recently, a genomewide scan for linkage revealed several susceptibility loci for AA. These suggest that a gene(s) on chromosome 18p [6, 10, 16] may be linked to AA and may be involved in other inherited skin and hair disorders as well [10].
1.5.12 Gene Therapy

Over the last two decades, substantial progress has been made in the field of molecular genetics in the identification of genes and the defects responsible for a wide spectrum of inherited skin diseases. To date, the therapy of genetic disease has been restricted symptomatic treatments and often these efforts are not effective. Although some genodermatoses can be tolerated throughout life, others can be lethal [100]. Therefore, the goal in the management of inherited diseases is a therapy, which can eliminate the underlying biochemical defect, rather than just treat the symptoms.

Traditionally, gene therapy was considered to be a potential approach for treatment of the more severe genodermatoses. This is an experimental technique that is designed to introduce the desired genetic material to the cells. Particularly, it can be used to compensate for a malfunction of a damaged gene via expression of a beneficial protein. In the inherited disorders where the mutation has been identified, the defective gene is an obvious target for the gene replacement therapy.

Researchers are also testing several other approaches. Replacing a mutated gene that causes disease with its healthy copy is just one of them. Inactivation of the gene that does not function properly is an alternative solution. Introducing a new gene into the body to help fight a disease could be another option [101].

Successful gene therapy requires efficient gene delivery to the malfunctioning organ, prolongation of gene expression, and potentially, suppression of the immune system. Using a carrier with an inserted copy of the therapeutic gene remains the most common approach for gene therapy. Additionally, the gene carrier, known as a vector, also contains some regulatory elements chosen from the gene sequence that allow the gene to be expressed in cells. The target cells can either be in culture (e.g., keratinocytes) (ex vivo) or reside in the organ or tissue (in vivo) (Fig. 1.5.2).

For example, to introduce genetic material directly into skin cells, skin sample from the patient must be taken, the keratinocytes or dermal fibroblasts must then be cultured in order for the genetic material to be introduced into these cells prior to regrafting them back into the patient. (Fig. 1.5.2a).

In vivo delivery requires injection of vectors into the affected tissue or by electroporation or using particle acceleration (“a gene gun”) (Fig. 1.5.2b) [102, 103].

There are a variety of vectors designed for gene therapy. The main types of vectors are viral and nonviral. Nonviral vectors contain naked DNA. For delivery, they have to be encapsulated in a vesicle made of cationic lipids (lipoplexes), which is attached to a polymer (polyplexes) or set of synthetic oligonucleotides. The major advantages of non–viral delivery systems are: (1) vectors are easily produced in large quantities and (2) they do not trigger an immune response. As opposed to viral vectors, nonviral vectors have poor transduction efficiency, especially when they are used in primary cells and their effect is limited in duration. To improve the nonviral vector approach few other strategies such as spliceosome-mediated RNA trans-splicing (SmaRT) [104, 105], C31 bacteriophage integrase [106], and the
Sleeping Beauty [107, 108] and Piggy Bac [109] transposon systems have been developed. To date, viral vectors have offered the most reliable strategy for gene therapy. Viral vectors originate from viruses that have been genetically altered to carry normal human DNA and to deliver genes into human cells where they can be expressed. Most often viral vectors are made from retroviruses and adenoviruses. Retroviruses have the greatest potential owing to their ability to integrate into the host genome where the genes of interest can be expressed. This is especially important for tissues with continuous regeneration, such as the epidermis, due to the fast turnover of the cells. Retroviral vectors are currently the only ones that can mediate efficient integration of a transgene into target cells and therefore achieve durable gene delivery through multiple cell cycles in tissues that undergo continual regeneration such as epidermis [110, 111]. Adenoviruses or viruses of the herpes family usually do not integrate their DNA into the host genome, and the level of gene expression therefore decreases over time. Viral-based methods are useful for expressing genes and producing short RNAs (shRNA) to knock down genes via RNA interference (RNAi).

The most obvious use of gene therapy is in the repair of a single defective gene as in inherited monogenic diseases. Especially in monogenic recessive inherited skin disorders such as junctional EB [112, 113] and X-linked or lamellar ichthyosis [114], a full phenotype reversion of the disease phenotype has been achieved in vivo, and for xeroderma pigmentosa, in vitro [115].

Dominant disorders, however, cannot be corrected simply by overexpressing the correct protein, because the aberrant protein synthesized from the mutant allele is still present. In these cases, a treatment strategy that results in the inhibition or elimination of the mutant allele selectively must be developed since simple gene replacement will not correct this kind of defect. One possibility is the use of short inhibitory RNA (RNAi) technology. This technique may be applicable to deactivate dominant-negative alleles by selective elimination of the mutation at the transcription level [116, 117]. Alternatively, in the so-called supplementation therapy approach, the defective gene is “by-passed” by inducing the expression of another gene with similar function, which is not affected by the mutation [118].

In the field of genetics, an understanding of mutated genes and the specific consequences of genetic mutations are crucial in the design of a targeted therapy. On the other hand, gene therapy can also be used to counter more complex diseases where the specific genetic aberrations are not known. One example is suicide gene therapy, which is used in cancer or hyperproliferative disorders by producing molecules that kill the recipient cells. The genetic vaccination technique delivers a gene product, which elicits an immune response.

Even without precise knowledge of the underlying genetic process, specific destruction of a targeting tumor can be achieved. For metastatic melanoma a large number of clinical trails have been performed using DNA, RNA or dendritic cell vaccinations with a mix of positive and negative results [119–121].

1.5.13 Naturally Occurring Gene Therapy: Revertant Mosaicism

Revertant mosaicism is a form of “natural gene therapy,” and refers to the rescue of the disease-causing mutation due to the natural occurrence of a second nullifying mutation. When a naturally occurring second mutation that rescues the disease causing mutation and restores, partially or completely, the wild-type phenotype by either genetic or nongenetic mechanism of reversion, this individual is called a revertant [122]. It gives rise to the idea of gene therapy and provides clues to optimal therapeutic gene manipulation.

If the rescue occurs in germline cells, this allele is transmitted to the offspring and they will not be affected or may be mildly affected. Such mutations return the activity of the mutated gene, but frequently lead only to a partial reversion [123].

If the reverse mutation occurs in somatic cells, just parts of the individual will be revertant. This phenomenon is called somatic revertant mosaicism.

There are a small number of reports of revertant mosaicism in skin disorders, with several different genetic mechanisms, the first one described in Lesch-Nyhan syndrome in 1988 [88, 124, 125]. The underlying revertant mosaicism can include mitotic gene conversion [65], splicing [125], back mutations (reverse point mutation), and second site mutations (base pair addition or deletion, suppressor mutation, and chromosomal loss...
or gain) [88]. In dermatology this mechanism was described on a molecular level in a patient with generalized atrophic benign EB [65].

It has recently been demonstrated that in vivo germline mutations can be corrected by multiple spontaneously occurring somatic mutations [126]. These revertant mutations must have occurred in epidermal stem cells, which not only give an example for natural gene therapy, but can also provide an excellent naturally corrected cell graft for transplantation to affected de-epidermized skin regions on the same patient, without the typical occurrence of immunologic graft rejections [127].

Revertant mosaicism is an example of natural gene therapy and validates the potential success of the gene correction that emerge by recombinational repair [128]. Further clarification of natural mechanisms in correcting gene mutations may provide new clues to devise targeted therapies for genodermatoses in the coming years.

### References

1. Bateson W (1907) “The Progress of Genetic Research”. In: Wilks W (ed) Report of the Third 1906 International Conference on Genetics: Hybridization (the cross-breeding of genera or species), the cross-breeding of varieties, and general plant breeding. Royal Horticultural Society, London. (although the conference was titled “International Conference on Hybridisation and Plant Breeding”, Wilks changed the title for publication as a result of Bateson’s speech)


### Take Home Messages

- Genetic disease may be caused by mutations in one gene (Mendelian or monogenic), more than one gene (polygenic), or as a result of combined interactions between environmental and genetic influences (multifactorial).

- The major single gene patterns of inheritance are autosomal recessive (Lamellar Ichtyosis), autosomal dominant (Darrier Disease), X-linked recessive (Menke’s Disease), and X-linked dominant (incontinentia pigmenti).

- Other factors affecting the basic Mendelian patterns include incomplete penetrance, variable expression, mosaicism, late onset or de novo mutations.

- Chromosomal abnormalities can be numerical (excess or loss of chromosomes) or structural (chromosomes rearrangements, deletions or duplications).

- The principle of gene therapy is to introduce therapeutic genetic material into target cells or tissue in order to compensate for abnormal genes or to make beneficial proteins. The delivery vector can be either viral or nonviral.


1.6 The Stratum Corneum (SC) as Skin Barrier

Among various protective functions of the skin, the barrier function is most vital to maintain a constant internal milieu from the ever changing outside environment [1]. Most of all, the skin must prevent evaporative loss of water that is essential to the fully hydrated viable tissues on this dry surface of the earth. Its barrier function, which is effective enough to interfere even with the passage of a small water molecule, also plays an important role in protecting our body from permeation of external injurious agents including ultraviolet light, needless to say about the invasion of much larger microorganisms including viruses. In contrast, it is difficult even for beneficial drugs or nutrients to be absorbed sufficiently through the normal skin.

This barrier function of the skin depends on the presence of the SC, an only-10 μm thick membranous...

---

**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC</td>
<td>Stratum corneum</td>
</tr>
<tr>
<td>TEWL</td>
<td>Transepidermal water loss</td>
</tr>
</tbody>
</table>

---

**Key Features**

- Those substances with a molecular weight larger than 500 Da can hardly penetrate through the skin covered by just a 10-μm thick SC as skin barrier.
- The SC barrier function depends on the presence of its unique intercellular lipids that are tightly bound to maturated corneocytes, whose formation is disturbed in diseased skin.
- The SC barrier function is not uniform and greatly differs among various body locations with extremely poor barrier function in the face and genital skin.
- The bypass pathway penetration through hair follicles and sweat ducts may allow quick but only small amount of penetration of externally applied substances.
- Excessive SC hydration induced by occlusion causes swelling of the corneocytes to lead to several to more than tenfold increase in percutaneous absorption of applied drugs.
- Normal SC binds water to keep the skin surface smooth and soft in contrast to pathologic SC with deficient water-binding capacity that produces a scaly or cracked skin surface.

---

Corneotherapy consisting of daily applications of a highly moisturizing agent not only induces long-lasting increase in skin surface hydration but also repairs mild SC barrier dysfunction such as noted in atopic xerosis.
structure present at its uppermost portion [2, 3]. When we remove the SC totally with tape stripping, there occurs free evaporation of water as well as penetration of even large molecular substances as observed in the mucous membranes.

### 1.6.2 The Structure of the SC as Skin Barrier

The SC has been likened to a brick wall, namely the corneocytes, the final protein-rich form of differentiated keratinocytes as bricks and intercellular lipids as mortar [2]. For the SC barrier function, the intercellular lipids are essential. They are composed of almost equal molecular amount of ceramides, cholesterol, and free fatty acids. They are produced in lamellar granules of differentiated keratinocytes by the action of their unique enzymes, being discharged from the granular cells into the intercellular space between the tightly interconnected corneocytes. After firmly binding to fully maturated cornified envelopes covering the corneocytes, they form a compact lamellar structure in the narrow intercellular space (Fig. 1.6.1). Thus, not only the composition of the intercellular lipids but also the maturity of corneocytes determines the integrity of the SC barrier function [2, 4]. When the epidermis increases its speed of differentiation as well as proliferation under the influence of various proinflammatory stimuli of endogenous or exogenous origin, there appear immature corneocytes even in the superficial portion of the SC together with an alteration in the composition of intercellular lipids, which results in the development of the SC with compromised barrier function [2].

### 1.6.3 In Vivo Evaluation of the SC Barrier Function

We can assess in vivo the SC barrier function by instrumentally measuring transepidermal water loss (TEWL) through the SC in the environment less than 22°C where no sweating takes place. The TEWL values of normal skin covering most parts of the trunk and extremities are around 5 g/m²/h. However, the skin is not uniform all over the body but it displays distinct anatomical characteristics. Thus, on the face and genitals, TEWL values are significantly higher than those on the trunk and extremities even in healthy individuals, reflecting unique features of their SC such as a smaller number of the cell layers, lower intercellular lipid content or higher ratio of immature corneocytes [4–7]. Their TEWL levels are comparable to those measured on the lesional skin of atopic dermatitis present on the limbs, which means that we can live without any special inconvenience by directly exposing our face as long as such a level of TEWL is maintained.
1.6 Percutaneous Absorption and Principles of Corneotherapy/Skin Care

The highest TEWL values, around 35 g/cm²/h are demonstrated on the vermilion border of the lips where the oral mucosa is directly exposed to the outside, which also constitutes the driest part on the body [5].

1.6.4 Percutaneous Absorption (or Percutaneous Penetration)

The skin does not absorb externally applied agent but there occurs only their skin penetration based on the concentration gradient (Fig. 1.6.2). Because the SC is the rate-limiting diffusion barrier for most chemicals including a small molecule such as water, the absorption through the skin occurs to a substantially lesser degree than through the mucous membranes. However, it can still afford beneficial effects for transdermal delivery of certain therapeutics. Furthermore, occasionally, there occur untoward cutaneous or even systemic side effects after prolonged applications of potent corticosteroids under occlusion. Even on a daily basis, we are facing a risk of exposure to immunogenic small molecular antigens that may induce allergic contact dermatitis after penetration into the skin. Based on the regional differences, allergic contact dermatitis to water-soluble antigens such as metals and vegetables occurs commonly on lipid-depleted sites such as the palms, whereas that to lipophilic antigens such as poison ivy is more likely to develop at other lipid–replete locations [2].

In general, the substances with a molecular weight larger than 500 Da can hardly permeate through the SC of the normal skin on the trunk and limbs [8]. However, much larger substances can permeate the lesional skin covered with pathologic SC whose barrier function is partially disrupted. It is well recognized clinically that the topically applied tacrolimus whose molecular weight is 822 Da exerts a beneficial effect on the facial lesion of atopic dermatitis, but not so effectively on the lesions present in other bodily locations.

1.6.5 Appendageal Penetration

Because the skin appendages such as the hair follicles and sweat ducts are not covered perfectly by the SC, even a small amount of protein can penetrate into the skin via such a bypass pathway [3]. Since they account for only 0.1–1% of the total skin surface depending on the body locations, the amount of substances that permeate through the bypass pathway into the skin never reaches a high level. However, patients with strong immediate hypersensitivity to a protein antigen may develop contact urticaria soon after its simple application on normal skin. In a similar fashion, the so-called atopy patch test conducted with environmental protein allergens can produce positive reactions even on nonlesional skin of the back of atopic dermatitis patients (Fig. 1.6.2). Of course, it is more reliable to conduct patch test on the skin whose barrier function is compromised with partial tape stripping or with needle scarification when we ascertain contact sensitivity for protein antigens such as fungal allergens in patients with superficial fungal infections [9, 10].

1.6.6 Occlusion

Because occlusion of the skin enhances permeation of various substances, it is often employed for transdermal drug delivery. Skin occlusion causes swelling of the corneocytes, which may provide an alternative penetration pathway not only through the cells but also through the intercellular lipid lamellae. Occlusion leads to several to more than tenfold increase in the percutaneous absorption, reflecting the chemical properties of the tested substances [3]. The majority of the past studies
investigating TEWL and percutaneous absorption have observed a quantitative correlation. However, those showing no correlation were all based on in vitro experiments using a diffusion cell that has an influence of occlusion to measure percutaneous penetration [11].

1.6.7 Influence of Vascularization

In addition to the SC permeability, the vascularization of the skin also plays an important role in percutaneous absorption. Although the facial skin displays poor barrier function as compared with the skin of the trunk and limbs, it is rich in vascularization, which quickly removes the absorbed substances from the tissues to reduce local adverse effects caused by irritants to some extent [12].

1.6.8 Water-Binding Capacity of the SC

The use of topical ointment remedies for the treatment of skin diseases is as old as medicine itself. Similarly, the usage of cosmetics started with human history. However, there has been a lack of definite scientific evidence for their beneficial effects on the skin.

In addition to the barrier function, the SC has another important function, namely, the SC can improve the quality of the skin surface by binding water to make it smoother and softer. Pathologic SC found in various dermatoses is deficient in water-binding substances such as intercellular lipids and small molecular water-soluble substances, the so-called natural moisturizing factor consisting of amino acids, lactate and urea. Thus, there develops dry and hard skin surface associated with scaling and fissuring.

1.6.9 Skin Care Products

The purpose of using cosmetics is mainly for the improvement of the skin appearance by supplying these substances to produce smoother and softer skin surface. Similarly, emollients that have been clinically used for the treatment of dry scaly skin surface exert an occlusive effect that increases skin surface hydration [9]. Recently, much more agreeable skin care products have been introduced in the form of creams and lotions for dermatological treatment of mildly scaly skin changes. However, as compared to topical drug therapy, the beneficial effects brought about by these skin care products have been regarded only evanescent, not being expected to have a long lasting effect.

1.6.10 In Vivo Assessment of Skin Surface Hydration

With the recent development of sensitive bioengineering techniques, it becomes possible to quantitatively evaluate the skin surface hydration [13]. Thus, not only the scaly lesional skin but those mildly abnormal skin such as pruritic dry skin noted in the nonlesional skin of atopic dermatitis patients or that develops in healthy elderly individuals in winter can be assessed objectively. Furthermore, it becomes clear that even clinically normal looking skin of young healthy individuals show significantly higher TEWL values as well as lower skin surface hydration state in winter than in summer if they are measured in the same environmental conditions [14], namely, the influence of the dry and cold winter environment is not only the induction of dry skin surface but it also deteriorates the SC barrier function. Moreover, dry skin easily produces cracks and fissures in the skin surface that decreases the threshold of itch sensation [15]. These skin surface changes induce scratching behavior to leave scratched wounds, which further exacerbate the itch-scratch cycles to facilitate the permeation of environmental allergens and to induce clinically observable eczematous changes in those who are contact-sensitive to them [16]. However, when we apply skin care cream or emollient to pathologic skin, they improve the dry skin and quickly reduce the itch sensation [15].

1.6.11 Corneotherapy

The efficacy of skin care products is not transient if it is assessed instrumentally. It is amazing that when the applications of highly moisturizing agents were repeated twice daily even for 5 days, the improvement of skin hydration was observable over the following 1 week [17].
Daily applications of such a moisturizing cream to the face of healthy individuals over 6 weeks in winter not only increased the skin surface hydration but also induced a reduction in the elevated TEWL together with an increase in the maturity of corneocytes even after 3 weeks of treatment [18]. Similar improvement of the functional properties could be induced in atopic xerosis with daily applications of a cosmetic cream base, indicating that maintenance of appropriate hydration state of the skin surface improves the barrier dysfunction of atopic xerosis that develops on the background of subclinical inflammation of the skin [19]. Therefore, even the treatment of minimally pathologic dry skin by SC moisturization with an appropriate skin care product, i.e., corneotherapy, is an important therapeutic modality to prevent its further exacerbation that will definitely occur under poor environmental conditions of dry and cold winter (Fig. 1.6.3).

**References**


**Take Home Message**

The percutaneous penetration of external agents hardly occurs in normal skin, but takes place rather easily through lesional skin showing SC barrier impairment. Corneotherapy consisting of daily repeated applications of skin care products not only increase skin surface hydration state to make the skin smooth and soft, but also improve mildly impaired barrier function as that found in xerotic skin that develops in cold and dry winter.

---

**Fig. 1.6.3** Mechanisms underlying corneotherapy

**Corneotherapy**

- Daily applications of moisturizing agents or emollients on the dry skin surface in a dry and cold environment in the wintertime

- Increase in the skin surface hydration state

- Repair of mildly impaired barrier function of the stratum corneum to prevent further development into secondary xerotic dermatitis or atopic dermatitis
moisturizers after their daily applications: evaluation of corneotherapy. Dermatology 220:308–313


1.7 Principles of Systemic Therapy

Lindy P. Fox

1.7.1 Introduction

This chapter describes the principles of systemic therapy for skin disease. The pharmacological principles and general considerations that guide the choice of systemic therapy for skin diseases will be discussed. The principles presented herein are intended as guidelines, the goal of which is to aid dermatologists in the selection of systemic therapies for their patients in a way that achieves the best clinical efficacy with the least possible toxicity. Bearing this in mind, each principle will be addressed from a general perspective, with examples given as they pertain to dermatology.

Key Features

- Systemic therapy for dermatologic disease is generally safe, but requires knowledge of the patient’s medical history, potential drug side effects, toxicity monitoring guidelines, and potential drug interactions.
- Identification of genetic polymorphisms in drug metabolism allows in some cases for predicting those patients at risk for adverse drug reactions.

1.7.2 Pharmacologic Principles of Systemic Therapy

The pharmacology of systemic therapy encompasses two areas, pharmacokinetics and pharmacodynamics [1]. Pharmacokinetics refers to a medication’s absorption, distribution, bioavailability, metabolism, and excretion. Metabolism, which will be discussed in more detail in several sections below, involves conversion of a drug (typically by the liver) from a lipophilic substance to a hydrophilic substance that can then be eliminated from the body (typically by the kidneys). Metabolism can be divided into two phases: Phase I includes hydroxylation, oxidation, and reduction reactions catalyzed by Cytochrome P450 (CYP) enzymes; Phase II reactions involve conjugation of the Phase I metabolic products with glucuronide, sulfate, or glutathione into polar, hydrophilic compounds ready for excretion [2, 3]. Pharmacodynamics refers to the mechanism of action of a drug. Understanding these basic principles and what influences them is essential in not only attaining therapeutic efficacy, but also in
Avoiding potentially harmful drug interactions and adverse effects. Pharmacogenetics, a subset of pharmacodynamics, is the study of how genetic variations influence an individual patient’s response to a drug [4]. As the principles of basic pharmacology are discussed in detail elsewhere in this text (see Chap. 1.3), pharmacology will be discussed here as it pertains to the choice and use of systemic therapies.

1.7.3 General Principles of Systemic Drug Therapy

Systemic drug therapy can be thought of as the art of administering a systemic medication to achieve clinical control of a disease while minimizing toxicity to the patient. Systemic medication use in dermatology faces inherent challenges. First, although dermatologists practice according to the best evidence available to them [5], randomized clinical trials and other rigorous evidence-based treatment algorithms are scarce in dermatology, leaving the dermatologist to look for additional guidance from reports and trials originating in the infectious disease, rheumatologic, oncologic, transplantation, surgical, and internal medicine literature. It is reassuring, however, to realize that dermatologists are actively participating in a multitude of efforts to address this paucity, some examples of which include developing multicenter randomized clinically controlled trials addressing systemic therapies for dermatologic diseases, devising standardized clinical rating scales to use in these trials [6], enlisting smaller pharmaceutical companies to aid in dermatologic drug development [7], and cultivating emerging disciplines such as dermatoepidemiology [5] and groups such as the Cochrane Collaboration and the Cochrane Skin Group [8]. Second, when prescribing systemic medications, physicians have the responsibility to ensure to the best of their ability, that no harm comes to the patient as a result of the intervention. The physician’s commitment to “do no harm” leads to a real, but perhaps exaggerated, fear of using a systemic therapy to treat dermatologic disease. While one must always consider the balance between the risks of adverse effects of a systemic medication vs. the risk of not treating with a systemic drug, this fear probably contributes to both the under-treatment and over-referral of patients with advanced or difficult to control dermatologic diseases away from community-based private practices to academic medical centers. Recognizing that the risk of a negative outcome with any intervention can never be “zero,” physicians can employ several strategies to minimize potential adverse effects of medications.

The initiation of systemic drug therapy in dermatology can be approached systematically: the physician determines that the patient’s disease warrants systemic therapy, decides that the patient is a good candidate for systemic therapy (reviews the patient’s medical history and performs the appropriate baseline laboratory and investigative tests), familiarizes him/herself with the disease being treated, evaluates the available treatment options, and, ultimately, matches the patient with the systemic drug that is most likely to lead to a good clinical outcome with the least amount of toxicity (Fig. 1.7.1).

When a physician evaluates available treatment options, the evidence supporting their use for a given skin condition, and their relative toxicities, he or she is, in effect, creating a therapeutic ladder for the treatment of that skin disease. The therapeutic ladder is useful in that it provides both a therapeutic starting point as well as sequential steps along which to proceed, should the patient not tolerate and/or the condition not respond to a given therapy. More often than not, as one moves “up” on the therapeutic ladder to more potentially toxic drugs, the better the clinical efficacy. In addition, as each patient is unique, factors such as compliance, coexisting medical conditions, and concurrent medications may make the therapeutic ladder for one patient look dramatically different from that of another patient with the same cutaneous disease.

---

**Fig. 1.7.1** Stepwise approach to systemic therapy

- Determine that the patient’s disease warrants systemic therapy
- Determine that the patient is a good candidate for systemic therapy
- Know the disease being treated
- Evaluate the available treatment options
- Match the patient with the systemic drug that is the most likely to lead to the best clinical outcome and least possible toxicity
1.7.3.1 When to Consider Systemic Therapy

In dermatology, the therapeutic ladder usually starts with a topical therapy and then proceeds to systemic therapy. Generally speaking, one considers using a systemic drug for the management of a dermatologic disorder when a disease entity confined to the skin fails to respond to topical therapy, topical therapy is not tolerated by the patient or is impractical given the extent of cutaneous involvement, the skin disease has associated internal organ involvement that cannot be treated with topical therapy alone, or the skin disease alone may potentially lead to significant morbidity and/or mortality if left untreated (Table 1.7.1).

1.7.3.2 Know the Patient

Matching the patient with the appropriate systemic medication requires a somewhat holistic approach to patient care. One must consider the patient’s motivation for systemic therapy, including the severity of the disease as seen through the eyes of the patient and the readiness of the patient to comply with the proposed treatment regimen and necessary laboratory monitoring. For example, for patients with mild-to-moderate papulo-pustular acne vulgaris, initial therapy with topical agents is a reasonable starting point. If the patient then fails topical therapy, systemic therapy with antibiotics may be introduced. In contrast, for a patient with severe papulopustular or disfiguring nodulocystic acne, systemic antibiotics followed by isotretinoin might be the more appropriate therapeutic ladder. However, in the United States (US), isotretinoin is contraindicated for a female patient of childbearing age who refuses to adhere to the standard US Food and Drug Administration approved iPLEDGE™ program for isotretinoin administration (Table 1.7.2).

Patient education and informed consent are also important factors in patient selection. Patients should be made aware of how to take the medication, modifications in lifestyle that may be required (e.g., avoiding alcohol while taking acitretin), the type of monitoring that is required (e.g., measuring renal function while on cyclosporine), potential common and serious adverse effects, how to recognize the signs and symptoms of adverse effects, and what types of intervention might be appropriate should adverse effects occur [1].

Table 1.7.2 How to maximize efficacy and minimize toxicity of a systemic medication

<table>
<thead>
<tr>
<th>Know the patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease severity as seen through the eyes of the patient</td>
</tr>
<tr>
<td>Ability to comply with treatment regimen and necessary laboratory monitoring</td>
</tr>
<tr>
<td>Ability to obtain the systemic medication (cost and availability of the medication)</td>
</tr>
<tr>
<td>Patient education</td>
</tr>
<tr>
<td>Informed consent</td>
</tr>
<tr>
<td>Medical history</td>
</tr>
<tr>
<td>Underlying medical conditions of the patient (see Table 1.7.3)</td>
</tr>
<tr>
<td>Polymorphisms in drug metabolism (see text)</td>
</tr>
<tr>
<td>Patient is a woman of childbearing age or is breastfeeding</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Know the skin disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical natural history of the disease</td>
</tr>
<tr>
<td>Morbidity and mortality of the skin disease</td>
</tr>
<tr>
<td>Is there evidence-based literature to guide medication choice?</td>
</tr>
<tr>
<td>Does the disease have a predictable and/or measurable response to certain systemic medications?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Know the medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identify absolute and relative contraindications to therapy with a certain drug (see Table 1.7.3)</td>
</tr>
<tr>
<td>Identify polymorphisms in drug metabolism before beginning therapy, where appropriate (see text)</td>
</tr>
<tr>
<td>Know the potential toxicities of a drug</td>
</tr>
<tr>
<td>Identify potential drug interactions (see Table 1.7.4)</td>
</tr>
<tr>
<td>Monitor patient for adverse effects</td>
</tr>
<tr>
<td>Check necessary laboratory tests during systemic therapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Additional strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Make adjustments in medication to keep toxicity low</td>
</tr>
<tr>
<td>Enlist help from other specialists when indicated</td>
</tr>
</tbody>
</table>

Table 1.7.1 When to consider initiating systemic therapy or moving up on a therapeutic ladder

<table>
<thead>
<tr>
<th>Topical therapies are not available, impractical for the given amount of cutaneous disease, or are ineffective in controlling disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease is reversible or controllable</td>
</tr>
<tr>
<td>A clinical response to therapy can be measured</td>
</tr>
<tr>
<td>The disease being treated is of substantial health risk to the patient if effective treatment is not started (i.e., the skin disease has associated internal organ involvement, is serious, or is life-threatening)</td>
</tr>
<tr>
<td>The least potentially toxic effective systemic therapy has been tried and failed</td>
</tr>
</tbody>
</table>
Informed consent implies that the physician and patient have discussed the following: the diagnosis; the proposed intervention, including potential risks, benefits, and limitations of the therapy under discussion; and alternatives to the proposed intervention (including no treatment) [1]. In addition, the patient should be given time to reflect on the discussion, ask questions, and perhaps request the physician’s expert advice [1]. After being thus informed, the patient and physician then make a joint decision on a course of therapy. Written documentation in a patient’s chart that this discussion has taken place is advocated. Furthermore, in cases of investigative therapies, very risky medications, or where federal regulation requires it (e.g., iPledge™ in the US), a patient’s signature in the chart may be required.

1.7.3.3 Know the Skin Disease

Before deciding to embark on a systemic therapy, it is imperative that the physician comprehend, to the best of his or her ability, the natural history of the skin condition for which the systemic therapy is being considered, including the morbidity and mortality of the disease and tendency for spontaneous remission vs. relapse and remittance. In addition, when available, evidence-based literature evaluating how a given skin disease responds to a specific medication should be sought. Ideally, the latter point is best determined through clinical trials conducted during drug development. As already mentioned, evidence-based data to guide the choice of systemic therapy in dermatology is more often based on clinical experience and anecdotal reports than randomized controlled clinical trials. Take the hypothetical case of a patient who is admitted to the hospital with generalized pustular psoriasis. Such a patient is nearly always in need of a systemic medication. Based on anecdotal reports and clinical experience, we know that both acitretin and cyclosporine are effective in the treatment of pustular psoriasis; all other variables being equal, cyclosporine might be a better choice for the patient described, as it has a faster onset of action. This conclusion, while probably clinically reproducible, is based on the combination of anecdotal reports and the clinical experience of long-term practitioners, not randomized controlled trials comparing these medications for the treatment of a hospitalized patient with generalized pustular psoriasis.

1.7.3.4 Know the Medication Under Consideration

1.7.3.4.1 Identify Absolute and Relative Contraindications to Systemic Drug Therapy

Because systemic medications used in dermatology often have the potential to affect one or a combination of the hepatic, renal, hematopoietic, nervous, ocular, musculoskeletal, pulmonary, or cardiac systems, the risk of adverse effects can be amplified in patients with underlying medical conditions. Knowledge of the baseline status of the organs responsible for metabolism and excretion of a medication as well as those potentially vulnerable to a certain drug is of utmost importance in selecting a systemic agent that will be least likely to result in a negative outcome (Table 1.7.3). For example, the thin, inactive patient placed on systemic corticosteroids might be more likely to develop corticosteroid-induced osteoporosis than one who is active and of average weight [1]. Methotrexate, metabolized primarily by the liver, is not the ideal choice for patients with significantly abnormal liver function tests at baseline, symptomatic liver disease, or evidence of hepatic fibrosis [1].

In certain cases, knowledge of potential adverse effects as they pertain to a patient’s medical history becomes realized with clinical experience with a drug. This is especially true for new classes of medications. For example, the tumor necrosis factor-α inhibitors are recent therapeutic advances in dermatologic therapy. Complications of therapy include infections, exacerbation of congestive heart failure, and multiple sclerosis-like syndromes; thus, therapy with TNF-α inhibitors is not recommended or should be used with extreme caution in patients with severe congestive heart failure, clinically important infections, including latent tuberculosis or fungal infections, or a history of central nervous system demyelinating diseases [9]. Importantly, worsening heart failure, reactivation tuberculosis, and other infections became evident only in postmarketing reports, a fact that serves to remind the clinician that guidelines for the use of systemic agents should be considered continuously subject to modification.

Pregnancy and women of childbearing potential are a special group of patients to consider when deciding upon systemic therapies. Systemic retinoids (e.g., acitretin, bexarotene, and isotretinoin), methotrexate, and
<table>
<thead>
<tr>
<th>Drug</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Pregnancy, lactation</td>
</tr>
<tr>
<td></td>
<td>Women or men of childbearing age</td>
</tr>
<tr>
<td></td>
<td>Liver disease</td>
</tr>
<tr>
<td></td>
<td>Abnormal liver function tests</td>
</tr>
<tr>
<td></td>
<td>Hepatitis B, C</td>
</tr>
<tr>
<td></td>
<td>Alcoholic liver disease</td>
</tr>
<tr>
<td></td>
<td>Hepatic cirrhosis</td>
</tr>
<tr>
<td></td>
<td>Renal disease – adjust dose</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>Hematologic abnormalities</td>
</tr>
<tr>
<td></td>
<td>History of active or latent infections (tuberculosis, others)</td>
</tr>
<tr>
<td></td>
<td>Immunodeficiency syndrome</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Significant renal insufficiency</td>
</tr>
<tr>
<td></td>
<td>Uncontrolled hypertension</td>
</tr>
<tr>
<td></td>
<td>Clinically cured or persistent malignancy</td>
</tr>
<tr>
<td></td>
<td>Active infections</td>
</tr>
<tr>
<td></td>
<td>Immunodeficiency</td>
</tr>
<tr>
<td></td>
<td>Pregnancy, lactation</td>
</tr>
<tr>
<td></td>
<td>Concurrent immunosuppression with other agent(s)</td>
</tr>
<tr>
<td></td>
<td>Concurrent medications that potentiate renal dysfunction or interfere with</td>
</tr>
<tr>
<td></td>
<td>cyclosporine metabolism</td>
</tr>
<tr>
<td>Retinoids (acitretin,</td>
<td></td>
</tr>
<tr>
<td>isotretinoin,</td>
<td>Pregnancy, women of childbearing age, lactation</td>
</tr>
<tr>
<td>bexarotene)</td>
<td>Hypertriglyceridemia or hypercholesterolemia (moderate to severe)</td>
</tr>
<tr>
<td></td>
<td>Significant hepatic dysfunction</td>
</tr>
<tr>
<td></td>
<td>Significant renal dysfunction</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism (bexarotene)</td>
</tr>
<tr>
<td></td>
<td>Leukopenia</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>Pregnancy, lactation</td>
</tr>
<tr>
<td>mofetil</td>
<td>Peptic ulcer disease</td>
</tr>
<tr>
<td></td>
<td>Renal insufficiency (adjust dose)</td>
</tr>
<tr>
<td></td>
<td>Hepatic insufficiency</td>
</tr>
<tr>
<td></td>
<td>Cardiopulmonary disease</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Pregnancy, women of childbearing age</td>
</tr>
<tr>
<td></td>
<td>Existing peripheral neuropathy</td>
</tr>
<tr>
<td></td>
<td>Significant hepatic dysfunction</td>
</tr>
<tr>
<td></td>
<td>Significant renal dysfunction</td>
</tr>
<tr>
<td></td>
<td>History of neurological disorders</td>
</tr>
<tr>
<td></td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>History of hypercoagulability, stroke</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Dapsone</td>
<td>Prior hypersensitivity to dapsone</td>
</tr>
<tr>
<td></td>
<td>Allergy to sulfonamide antibiotics</td>
</tr>
<tr>
<td></td>
<td>G6PD deficiency</td>
</tr>
<tr>
<td></td>
<td>Significant cardiopulmonary disease</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Systemic fungal infections</td>
</tr>
<tr>
<td></td>
<td>Hypertension, congestive heart failure</td>
</tr>
<tr>
<td></td>
<td>History of psychosis or depression</td>
</tr>
<tr>
<td></td>
<td>Peptic ulcer disease</td>
</tr>
<tr>
<td></td>
<td>Active or latent tuberculosis</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>Cataracts or glaucoma</td>
</tr>
</tbody>
</table>

(continued)
thalamide, are all pregnancy category X and used with some frequency in dermatology. Knowledge of a female patient’s childbearing potential and future plans for childbearing are all essential prior to embarking on systemic therapy with one of the aforementioned medications. Furthermore, in the US, drug administration to women of childbearing age is highly regulated for certain medications (e.g., iPledge™ for isotretinoin, S.T.E.P.S.® program for thalidomide). Similarly, precautions should be undertaken for women who are breastfeeding. In such circumstances, it may be prudent to hold systemic medications until the patient is no longer breastfeeding. Conversely, in a situation where the systemic medication is considered life-saving (a rare, but potential occurrence in dermatology) breast feeding may be stopped in favor of embarking on life-saving systemic treatment.

**1.7.3.4.3 Cytochrome P450 (CYP)**

A major enzymatic system involved in drug metabolism is the cytochrome P450 (CYP) family of enzymes

---

Table 1.7.3 (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td>Pregnancy, Allopurinol use (adjust azathioprine dose), Active infections, Prior use of alkylating agents</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Pregnancy, lactation, Bone marrow suppression, Clinically significant infections, Renal insufficiency, Hepatic insufficiency</td>
</tr>
<tr>
<td>Antimalarials</td>
<td>Hypersensitivity, Pregnancy and lactation, Severe blood dyscrasias, Significant hepatic dysfunction, Significant neurological disorders, Retinal or visual field changes, Psoriasis</td>
</tr>
<tr>
<td>Intravenous immunoglobulin</td>
<td>IgA deficiency, Progressive renal dysfunction, Pregnancy, History of hypercoagulability, stroke</td>
</tr>
<tr>
<td>TNF-α inhibitors</td>
<td>Congestive heart failure, Clinically important infections, chronic or recurrent infections, latent tuberculosis or fungal infections [9], History of central nervous system demyelinating disease</td>
</tr>
</tbody>
</table>

Adapted from refs. [1, 9]
that resides mainly in the liver. This enzyme superfamily is responsible for the first step in enzymatic oxidation of harmful lipophilic drugs (substrates) to inactive hydrophilic metabolites that are then eliminated by the kidney [3]. Most of the clinically important polymorphisms in CYP enzymes reside in 6 isozymes: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4, with CYP2D6 and CYP3A4 representing the most significant polymorphisms in humans [11, 12]. Familiarity with CYP enzymes is most important in anticipating drug interactions (see below). However, it is important to recognize that CYP-associated variability in metabolism can lead to drug accumulation and toxicity, activation of drugs to toxic metabolites, lack of activation of a prodrug, or rapid metabolism, and clearance of the drug with minimal therapeutic effect [4]. Indeed, certain CYP enzyme polymorphisms that account for altered drug metabolism are becoming increasingly recognized [4] and DNA-based testing to identify polymorphisms in some CYP enzymes (e.g., CYP2D6 and CYP2C19) have been developed [11].

1.7.3.4.4 N-Acetyltransferase (NAT)

Drugs that are metabolized by the enzyme NAT will be variably metabolized in the presence of polymorphisms at the NAT2 gene locus. A variety of polymorphisms at NAT2 exists and correlates with either a rapid or slow acetylator phenotype [12]. Patients who possess the rapid acetylator alleles will metabolize a drug that depends on NAT more quickly, thereby deriving a less therapeutic effect of that drug. Conversely, those who possess the slow acetylator phenotype will metabolize a substrate of NAT more slowly and be at higher risk for toxicity. Examples relevant to dermatology are sulfonamide induced Stevens-Johnson syndrome and toxic epidermal necrolysis. Both Stevens-Johnson syndrome and toxic epidermal necrolysis due to administration of a sulfonamide have been associated with the slow acetylator phenotype, although this genotype alone (which is present in 40–70% of Caucasian population) is thought not to be sufficient to induce these reactions [4, 12, 13]. Also worth mentioning is the finding that patients who are infected with the human immunodeficiency virus (HIV) may have a greater chance of possessing a slow acetylator phenotype than non-HIV infected patients [12].

1.7.3.4.5 Thiopurine S-Methyltransferase (TPMT)

The metabolism of azathioprine is complex. Azathioprine, the parent drug, is converted to 6-mercaptopurine (6-MP). 6-MP is then metabolized by three competing enzymes, xanthine oxidase (XO), TPMT, and hypoxanthine phosphoribosyl transferase (HPRT) [14] (Fig. 1.7.2).

XO and TPMT are responsible for catabolizing 6-MP into nontoxic metabolites, while HPRT is involved in the pathway that converts 6-MP to its active toxic purine analog 6-thioguanine (6-TG). Single nucleotide polymorphisms in the wildtype, highly active TPMT gene, are inherited as an autosomal codominant trait and result in various activity phenotypes of the enzyme: 1 in 220 patients have no enzyme activity, 10% have low activity, 80% have normal activity, and 9% have high activity [9, 14, 15]. If azathioprine is given to a patient with low TPMT activity, accumulation of toxic thioguanine nucleotides occurs, resulting in myelosuppression. Fortunately, there are assays that can determine a patient’s TPMT phenotype prior to beginning azathioprine, so that the azathioprine dose can be adjusted accordingly [1, 14].
1.7.3.4.6 Glucose-6-Phosphate Dehydrogenase (G6PD)

A base pair substitution (asparagine to aspartic acid) in the gene encoding the enzyme G6PD accounts for low levels of G6PD enzyme activity. Patients with G6PD deficiency abnormally metabolize dapsone and hydroxychloroquine, substantially increasing the risk of hematolytic anemia in this subgroup [12]. G6PD levels should therefore be assessed prior to beginning therapy with either of these agents in order to minimize potential drug toxicity.

1.7.3.4.7 Know the Adverse Effect Profile of the Medication Under Consideration

An adverse effect, or side effect, of a medication is the most common cause of iatrogenic disease [16]. An adverse effect can be defined as a negative or undesirable effect (either toxic or pharmacologic) from a drug [1]. A pharmacologic effect of a drug is the positive or negative effect of a drug that is expected at normal doses and/or drug levels [1]. An example is cheilitis as an expected side effect of isotretinoin. Toxicity refers to an undesirable, but expected, effect of a drug that occurs in all patients at excess doses or levels of drug [1]. An example is liver toxicity due to excessive doses of acetaminophen. Idiosyncratic reactions are unexpected and result from an interaction between the drug and unique host factors, some of which are genetically (i.e., metabolically or immunologically) or environmentally determined [1, 16]. The anticonvulsant hypersensitivity reaction is an example of an idiosyncratic drug reaction.

The therapeutic window of a drug refers to its range in plasma concentration between that which results in clinical efficacy and that which results in toxicity [16]. A narrow therapeutic window means that there is a small range between the therapeutic and toxic plasma concentrations of a drug. Drugs that have a narrow therapeutic index have a higher risk of toxicity. In dermatology, it is important to be familiar with the systemic medications that have a narrow therapeutic index (e.g., cyclosporine). It is also important to note that because of potentially great variations in pharmacodynamics in humans, the dose or concentration of a drug required to achieve a desired clinical effect in one part of a population often overlaps with the dose or concentration that results in toxicity in another segment of the population [16].

As mentioned above, systemic medications used in dermatology often have the potential to affect one or a combination of other organ systems, most commonly the liver and kidney. It is essential that the physician is familiar with a drug’s adverse effect profile as well as when in the treatment course an adverse event due to a given drug is likely to occur. Prior to beginning systematic therapy, the patient should be made aware of the signs of adverse effects and when to bring them to the attention of a physician. In addition, it is prudent to try to avoid using systemic medications with overlapping toxicities (e.g., minocycline and isotretinoin may lead to pseudotumor cerebri). When possible, physicians should also implement interventions to prevent adverse effects (e.g., the administration of calcium, Vitamin D, and bisphosphonates to a patient on long-term corticosteroid therapy [1]; counseling a patient to use a broad spectrum sunscreen and practice sun avoidance during doxycycline therapy).

1.7.3.4.8 Minimize Potential Drug Interactions

Most patients who receive multiple systemic medications do not experience adverse effects. Patient risk factors that increase the risk for drug interactions include the intake of three or more systemic medications, very young or elderly patients, female sex, major organ dysfunction, metabolic or endocrine disorders (obesity, hypothyroidism, hypoproteinemia), slow acetylator phenotype, genetic polymorphisms in enzymes involved in drug metabolism, hypothermia, hypotension, and dehydration [17].

The mechanisms of drug interactions can be characterized as either pharmacokinetic (i.e., one drug interferes with absorption, distribution, metabolism, or excretion of another drug) or pharmacodynamic (i.e., one drug induces a change in another or two drugs compete for receptor binding) [18]. Table 1.7.4 outlines several examples of drug interactions important in clinical dermatology. The majority of clinically significant drug interactions in dermatology involve pharmacokinetics, specifically, alterations in drug metabolism. An example of one drug interfering with the metabolism of another is the co-administration of allopurinol and azathio-prine. Allopurinol works through the inhibition of XO (Fig. 1.7.2). However, the metabolism of azathioprine
<table>
<thead>
<tr>
<th>Pharmacokinetic step</th>
<th>Mechanism</th>
<th>Notable features</th>
<th>Selected examples of some interactions relevant to dermatology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Formation of drug complexes</td>
<td>Administering the listed drugs with polyvalent cations (antacids, calcium supplements, iron, zinc, multivitamins, sucralafate, and dairy products) results in decreased bioavailability [30]</td>
<td>Tetracycline, mycophenolate mofetil, fluoroquinolones, bisphosphonates</td>
</tr>
<tr>
<td>Alteration in gastric pH</td>
<td>Alteration in gastric pH</td>
<td>When drugs requiring an acidic milieu are administered with antacids, proton pump inhibitors, or H2 antagonists, the result is decreased absorption</td>
<td>Itraconazole, ketoconazole</td>
</tr>
<tr>
<td>Change in gastrointestinal motility and/or transit time</td>
<td>Change in gastrointestinal motility and/or transit time</td>
<td>Warfarin administered with cholestyramine leads to decreased absorption of warfarin</td>
<td></td>
</tr>
<tr>
<td>P-Glycoprotein [17]</td>
<td>Normally blocks absorption in the GI tract by controlling the rate of drug absorption; inhibition of p-glycoprotein results in increased absorption of substrate drugs</td>
<td>Substrates</td>
<td>Inhibitors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colchicine, Erythromycin, Ivermectin, Fluoroquinolones, Rifampin, Quinine, Methotrexate, Indinavir, Nelfinavir, Ritonavir, Saquinavir, Cyclosporine, Tacrolimus, Cimetidine</td>
<td>Clarithromycin, Erythromycin, Itraconazole, Ivermectin, Ketoconazole, Ofloxacin, Rifampin, Amitriptyline, Doxepin, Cyclosporine, Tacrolimus, Grapefruit juice, Orange juice isoflavones, Ritonavir</td>
</tr>
<tr>
<td>Distribution</td>
<td>Alteration in protein binding</td>
<td>Often transient and therefore effect is negligible unless drug has a limited distribution, is slowly eliminated, or has a narrow therapeutic index</td>
<td>Methotrexate administered with sulfonamides causes displacement of methotrexate from plasma proteins, leading to increased circulation of methotrexate and higher risk of bone marrow suppression</td>
</tr>
</tbody>
</table>

(continued)
Table 1.7.4 (continued)

<table>
<thead>
<tr>
<th>Pharmacokinetic step</th>
<th>Mechanism</th>
<th>Notable features</th>
<th>Selected examples of some interactions relevant to dermatology&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism</td>
<td>Cytochrome P450 enzymes</td>
<td>Most clinically important drug interactions involve cytochrome P450 enzymes, specifically CYP3A4</td>
<td>Substrates&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Amitryptiline</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Atorvastatin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chloroquine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cyclosporine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dapsone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Doxepin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Enalapril</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fexofenadine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hydroxychloroquine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Loratadine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lovastatin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Retinoic acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sildenafil</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Simvastatin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Warfarin</td>
</tr>
<tr>
<td></td>
<td>Other enzymatic pathways</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Azathioprine given in combination with allopurinol-inhibition of xanthine oxidase by allopurinol leads to an increased risk of azathioprine toxicity</td>
</tr>
<tr>
<td>Excretion</td>
<td>Altered renal excretion</td>
<td></td>
<td>Methotrexate given in combination with nonsteroidal anti-inflammatory drugs inhibits renal excretion of methotrexate which increases the risk of bone marrow suppression</td>
</tr>
</tbody>
</table>

<sup>a</sup>This table is not intended to serve as a complete reference, but rather to illustrate to the reader the scope of potential adverse drug interactions as they pertain to systemic drug use in dermatology

<sup>b</sup>Substrate drugs are defined here as drugs that directly cause morbidity or mortality because of increased toxicity or decreased efficacy [18]

<sup>c</sup>Inhibitor drugs are defined here as drugs that inhibit the activity of a cytochrome P450 enzyme [18]

<sup>d</sup>Inducer drugs are defined here as drugs that induce the activity of a cytochrome P450 enzyme [18]
relies in part on XO. The concomitant administration of these medications results in increased shunting of 6-MP through alternative pathways, resulting in increased azathioprine toxicity [14].

The most common reason for alterations in drug metabolism involves the cytochrome P450 (CYP) family of enzymes (see above). Drug interactions mediated by CYP typically occur because the CYP-dependent metabolism of a substrate drug is either inhibited or induced by a concurrently administered medication. (The “substrate” drug is the drug metabolized by CYP. It is also the drug whose toxicity is enhanced or efficacy diminished by the coadministration of a CYP “inhibitor” or “inducer” drug, respectively [18]). The ultimate result of CYP inhibition or induction is increased toxicity and/or decreased efficacy of the substrate drug, the degree of which depends on (1) competitive or non-competitive binding of CYP, (2) each drug’s affinity for CYP, (3) the relative concentration of the drugs, and (4) the half-life of the drugs [2, 17, 18]. Inhibition of CYP results in higher plasma levels of a drug. Increased plasma concentrations of a drug may lead to an increased response, an increased risk of drug toxicity, or both. CYP inhibition is especially concerning during administration of a drug with a narrow therapeutic index. In contrast to inhibition of CYP, induction of CYP by a drug leads to increased activity of that enzyme. The time required for a drug to induce CYP depends on the half-life of the drug, but at least a week is typically required before the effects of enzyme induction become evident [18]. The more rapidly a drug is metabolized, the more rapidly it is excreted and the less therapeutic effect the drug will have. A drug interaction due to induction of CYP might therefore account for “failure” of a systemic medication for the treatment of a disease expected to respond to a given systemic therapy.

Although knowledge of the substrates, inhibitors, and inducers of the CYP enzymes aids in the prediction of drug interactions, clinical reports of drug interactions, including postmarketing data, remain the best evidence that a potential interaction between two drugs exists. This is because in vitro studies might not accurately predict drug interactions in clinical settings where medications can have complex metabolism and/or patients are taking multiple medications concurrently [17, 18].

On occasion, drug interactions can be used to the prescriber and patient’s advantage. For example, as a substrate of CYP3A4, cyclosporine is susceptible to inhibition of CYP3A4 by grapefruit juice; it has therefore been suggested that taking cyclosporine with grapefruit juice might reduce the total dose (and cost) of cyclosporine, although this approach has been debated [2]. As another example, physicians may suggest that patients take ketoconazole [19] or itraconazole [20] with an acidic beverage in order to increase absorption of the drug in the gastrointestinal tract.

### 1.7.3.4.9 Monitor for Toxicity During Therapy

Drugs with the potential to impact organs such as the liver, kidneys, eyes, lungs, and nervous system often require monitoring prior to beginning and during therapy. Physicians should be aware of standard monitoring guidelines when available for administering systemic therapies. In general, patients at the initial point in their therapy, those who are “high risk,” or those who have abnormal test results, might require more frequent monitoring than “low risk” patients with normal and stable laboratory tests on standard doses of systemic therapies [1].

As mentioned earlier, knowledge of the baseline status of the organs responsible for metabolism and excretion of a medication as well as those potentially vulnerable to a certain drug is essential to both choosing the drug with the least likelihood of adverse effects (see underlying medical conditions of the patient, above) as well as establishing a baseline against which further testing during therapy will be compared. In addition, identification of genetic polymorphisms that may put a patient in a “high risk” group should be performed, where available (see Sects. 1.7.3.4.2 and 1.7.5). It is also important to note that monitoring guidelines not only change over time, but also differ between countries (see Sect. 1.7.5).

Prior to beginning therapy with cyclosporine (as an example), a patient’s baseline medical history, blood pressure, complete blood count, renal function (serum creatinine on two occasions), serum chemistries (including blood urea nitrogen, electrolytes, magnesium), liver function tests, serum lipid panel, and uric acid should be obtained. If these are within normal limits and cyclosporine therapy is initiated, then follow-up monitoring should be performed at 2 weeks, 4 weeks, and monthly thereafter, and includes a history (including new medications), physical examination (including blood pressure monitoring), renal function (serum creatinine and blood urea nitrogen), serum chemistries
(including electrolytes, magnesium), liver function tests, and uric acid level [21].

Systemic therapy with methotrexate for the treatment of psoriasis also serves to illustrate several important points of systemic drug monitoring in dermatology. Patients with normal baseline hepatic function and no other contraindications to methotrexate therapy require regular liver function tests while receiving chronic methotrexate therapy. However, even in this low risk group of patients, careful monitoring of liver function tests is necessary but may not be adequate to identify early hepatic fibrosis. Consequently, current practice guidelines recommend a liver biopsy when the cumulative methotrexate dose reaches 1.0–1.5 g [22]. A baseline liver biopsy also is recommended for those patients with increased potential risk for hepatic fibrosis, such as a history of alcohol abuse or infection with hepatitis B or C [22]. Measurement of serum procollagen III aminopeptide during methotrexate is discussed in Global Variations below.

1.7.3.4.10 Make Adjustments to the Treatment Regimen to Decrease Toxicity or Increase Clinical Response

During a course of systemic drug therapy, adjustments to the treatment regimen to either decrease toxicity or increase the clinical response to therapy can be made. Combination therapy is a useful technique to help minimize the risk of drug toxicity and/or maximize clinical efficacy. When a systemic therapy is initiated, concomitant topical therapy not only helps to control the skin condition until the systemic therapy takes effect, but might also help keep the overall dose of the systemic therapy lower than it would be otherwise. Topical therapy can also allow treatment of isolated areas of recalcitrant disease (e.g., a stubborn plaque of psoriasis) or minor fluctuations in disease control (e.g., a “breakthrough” blister of bullous pemphigoid) during systemic treatment and thus aid in avoiding escalating doses of systemic drugs. Combining one systemic therapy with two or more other systemic therapies that have synergistic effects or complementary adverse effect profiles can minimize the doses and toxicities of each drug [23]. For example, treating psoriasis with the combination of low dose cyclosporine (<3 mg/kg/day) and low-dose methotrexate (<10 mg/week) allows for gaining clinical control of the disease at doses typically lower than the traditional monotherapy doses of either drug [23]. Combination therapy within or between drug classes can also be used to achieve clinical response when monotherapy is ineffective or only partially effective. For example, patients with dermatomyositis who do not fully respond to single agent antimalarial therapy with hydroxychloroquine or chloroquine may benefit from the addition of quinacrine [24].

As the main goal of systemic therapy is control of disease, it makes sense that once disease control is achieved the physician attempts to either find the lowest dose of a given medication that maintains clinically acceptable disease control or bridges systemic therapy to a drug or combination of drugs with a more favorable side effect profile. The rapidity with which a medication can be tapered or therapy can be bridged depends not only on the natural history of the condition being treated and the medication being used to treat that disease, but also on the patient’s ability to tolerate that medication. The treatment strategy for pemphigus vulgaris is a good example of this practice. Before the advent of corticosteroids, pemphigus vulgaris was a life-threatening disease. Currently, however, complications of systemic therapy (often systemic corticosteroids), not the primary disease, are the most common causes of morbidity and mortality associated with pemphigus vulgaris [25]. Thus, a reasonable algorithm for the treatment of pemphigus vulgaris is the induction of remission with systemic corticosteroids and the maintenance of disease control with a steroid sparing agent such as mycophenolate mofetil.

Take Home Message

Systemic therapy for dermatologic disease is safe, but requires a multilevel approach to patient care.

1.7.3.4.11 Enlist Help of Outside Specialists

Involving outside specialists to assist in the choice of systemic therapy and help monitor patients while on therapy is of utmost importance. The above example of ophthalmologic examinations during hydroxychloroquine therapy illustrates this point.
1.7.5 Global Variations

Variations in the approach to systemic therapy do vary globally. Examples include variations in the threshold at which one chooses to use systemic over topical therapy, the choice of a particular systemic drug for a disease where several therapeutic options exist, the prevalence of polymorphisms that affect drug metabolism in different ethnic populations, and different monitoring guidelines that exist in different areas of the world.

Genetic polymorphisms in drug metabolism are probably the most highly studied. As mentioned earlier, the presence of certain genetic polymorphisms may explain a particular patient’s beneficial response, failure, adverse reaction, or toxicity to a medication. For example, we now know that (1) The “slow acetylator” phenotype, which is a risk factor for developing sulfonamide-induced toxic epidermal necrolysis or Stevens-Johnson syndrome, represents more than 90% of some Mediterranean populations but only 10% of the Japanese population [4]; (2) Six percent of Caucasians, 16% of African Americans, 3% of Croatians, 8.3% of Polish, and 0.1% of Asians are homozygous for nonfunctional CYP2D6, a cytochrome P450 enzyme responsible for the metabolism of 25% of commonly prescribed medications [26]; (3) The highest prevalence of G6PD deficiency, which decreases a patient’s ability to tolerate sulfo-namides, and antimalarial agents, is highest in Indians, African Americans, and Nigerians [26]; (4) Normal activity of thiopurine methyltransferase (required for the metabolism of azathioprine) is more likely in Chinese than Caucasian American or Italian patients [26].

It is also important to note that monitoring guidelines differ between countries. For example, ophthalmologic testing for hydroxychloroquine therapy differs between the US and the UK. Prior to beginning hydroxychloroquine therapy, a baseline ophthalmologic examination, including slit-lamp (US), visual acuity (US and UK), and funduscopic (US and UK) examinations, are suggested [27, 28]. In the US, it is recommended that patients undergo a follow-up ophthalmologic examination every 6 months for the first year and yearly after that, with repeated examinations if patients complain of visual deficits or note “fading” on Amsler grid scales [28]. In contrast, follow-up in the UK, provided that the dose of hydroxychloroquine does not exceed 6.5 mg/kg/day, consists of questioning the patient about visual problems at each clinic visit and assessment of visual acuity yearly [27, 28]. This assessment does not need to be performed by an ophthalmologist unless problems are suspected or therapy with hydroxychloroquine exceeds 5 years [27, 28].

As another example, the use of serum procollagen III aminopeptide to predict patients with hepatic fibrosis due to long-term methotrexate therapy for psoriasis varies between nations [29]. While a European study has advocated that serial normal serum procollagen III aminopeptide levels can prevent unnecessary liver biopsy in this subset of patients [29], this practice is not widely used in the US.

References

Vitamin A is obtained from the diet mainly in the form of inactive precursors and the major body retinoids are retinaldehyde, retinol, and retinoic acid. Retinylesters and β-carotene are ingested and converted to retinyl esters for storage, mainly in the stellate cells of the liver. Demand for retinol results in the release of retinol–retinol binding protein complexes which are taken up by human skin. The storage of retinol in human skin occurs through esterification mediated by lecitin:retinol acyltransferase (LRAT) and the highest esterifying activity is found in the basal layer of the epidermis [1]. Hydrolysis of retinyl ester to retinol is regulated by a specific retinyl ester hydrolase (REH). Retinoic acid is derived from retinol precursors by conversion to retinaldehyde by alcohol dehydrogenase (ADH) or short-chain dehydrogenase/reductase (SDH) and subsequently to retinoic acid by retinaldehyde dehydrogenase activity (ALDH). Because cleavage of β-carotene involves retinal as an intermediate product it can function as a precursor for retinoic acid in epidermal cells (Fig. 1.8.1) [2, 3].

All-trans retinoic acid is thought to be the major "natural ligand" of all three nuclear RARs. In human skin, the primary metabolite of all-trans RA is 4-hydroxy all-trans retinoic acid, which is further metabolized to functionally active 4-oxo all-trans retinoic acid [4, 5]. Several pathways are involved in the

**Key Features**

- Human skin is capable of retinoid metabolism and storage.
- Human epidermis expresses retinoic acid receptors (RAR-γ > RAR-α) and retinoic X receptors (RXR-α > RXR-β) and is therefore responsive to retinoid treatment.
- Nonaromatic, monoaromatic and polyaromatic retinoid derivatives are used for systemic and topical treatment of various skin disorders.
- Systemic retinoids are highly teratogenic and application of topical retinoids should be avoided altogether during pregnancy.
- Country-specific approvals and recommendations have to be consulted before applying retinoid containing drugs.
metabolic transformation of retinoic acid, especially specific cytochrome P450 (CYP) enzymes such as CYP26A1 and CYP2S1 [6, 7]. Strong constitutive expression of CYP26A1 occurs primarily in basal epidermal keratinocytes (Fig. 1.8.2), as well as in eccrine sweat glands and sebaceous glands verifying the capacity of human skin to metabolize retinoic acid [6]. Cellular retinol-binding proteins (CRBP I/II) and cellular retinoic acid-binding proteins (CRABP I/II) are thought to be involved in the trafficking of retinoids and regulate their availability in the nucleus [8]. Retinoids affect keratinocyte proliferation and maturation via their binding to nuclear retinoic acid receptors (mainly (RAR) alpha and gamma) which form heterodimers with the 9-cis-retinoic acid receptor, retinoid X receptor (RXR) alpha [9]. Human epidermis expresses transcripts for RAR-α, RAR-γ, RXR-α, and RXR-β. Total RXR protein levels are fivefold greater than RAR total protein levels. Among RXR proteins, nearly 90% is RXR-α, with RXR-β minimally detectable and RXR-γ undetectable. Thus, among RAR proteins, nearly 90% is RAR-γ, with approximately 10% RAR-α and no detectable RAR-β [10]. Epidermal keratinocytes from normal skin display similar nuclear localization of all three receptors; RAR-α was detected with decreasing intensity from basal to suprabasal layers, RAR-γ showed the opposite trend, whereas RXR-α was uniformly expressed throughout the epidermis [9].

Thus interconversion, storage, uptake, metabolism, efflux and binding to specific receptors are factors determining the effects of retinoids on human skin cells as well as in the body. Under physiological conditions, the highest metabolizing and esterifying capacities are found in the basal cell layer of the epidermis, suggesting that retinoid levels are higher in the lower epidermis, which is closer to perfusate from dermal capillaries [3].

1.8.2 General Therapeutic Outline

Retinoids are currently used for topical or oral administration either as mono therapy or in combination with other drugs or physical modalities such as ultraviolet (UV) light. Topical therapy is recommended for treatment of several skin diseases including acne vulgaris, gram-negative folliculitis and acne rosacea. At least one topical retinoid, tazarotene, has been approved by the FDA for the treatment of plaque psoriasis [8]. Systemic administration of retinoids such as isotretinoin or acitretin is used for the treatment of acne and a number of disorders of keratinization including different forms of ichthyosis, psoriasis, pityriasis rubra pilaris, Darier’s disease, discoid lupus erythematosus and lichen planus.

1.8.3 Current Established Therapies

Vitamin A and its naturally occurring and synthetic derivatives, collectively referred to as retinoids, exert a wide variety of profound effects in embryogenesis, reproduction, regulation of inflammation, growth and differentiation of normal as well as tumor cells. Thousands of retinoid acid analogs have been synthesized, of which three generations have been established for systemic and topical treatment of various skin disorders:

- The nonaromatic retinoids: e.g., provitamin A (β-carotene), tretinoin (all-trans-retinoic acid) and isotretinoin (13-cis-retinoic acid)
- The monoaromatic retinoid derivatives: e.g., etretinate (trimethyl-methoxyphenyl analog of retinoic acid) and acitretin (9-(4-methoxy-2,3,6-triethyphenyl) -3-2,4,6,8-nonatetraenolic acid)
• The polyaromatic retinoid derivatives: e.g., tazarotenic acid 6-[2-(4,4-dimethyl-thiochroman-6-yl)-ethynyl] nicotinate and adapalene (6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthoic acid)

1.8.4 Retinol and Retinaldehyde

Because of their controlled conversion to retinoic acid or their direct receptor- independent biologic activity, retinaldehyde, retinol and retinyl esters are often used as cosmeceuticals. Retinol and retinyl esters are nonirritants and demonstrate only modest clinical efficacy. Topical retinaldehyde is generally well tolerated in 0.1 and 0.05% preparations and seems to be the most efficient cosmeceutical retinoid [11]. It may ameliorate oxidative stress [12], has an antibacterial activity by reacting nonenzymatically with cutaneous bacterial flora [13], and is expected to be helpful in epidermal regeneration [16], acting as UV-filters [14] and improving skin aging and photoaging [13, 15, 16]. Some of these effects could be due to nongenomic receptor-independent biologic actions [13, 14]. Retinol and retinyl esters account for more than 99% of endogenous total cutaneous retinoids (approximately 1 nmol/g) whereas retinaldehyde and retinoic acid are not detectable [17]. Consistent with the metabolic pathway shown in Fig. 1.8.1, retinaldehyde has a stronger retinoid-like activity compared to retinol; the activity of retinyl esters is even lower. Accordingly, the ranking order for skin tolerability is the opposite [13]. The clinical efficacy of 4-oxo-retinoids such as 4-oxo-retinaldehyde (0.05%) in mouse models is currently under investigation [13].

1.8.4.1 Tretinoin

Topical retinoids have been used for treating acne vulgaris since 1962, and the first substance to be studied was tretinoin [18, 19]. Topical retinoids can lyse mature comedones, reduce microcomedone formation and exert immunomodulatory effects [19]. Topical retinoids such as tretinoin and adapalene are used as first line and long-term treatment of either noninflammatory or inflammatory acne. Depending on country and indication, tazarotene, isotretinoin, motretinide and retinaldehyde are also available for acne treatment [19, 20]. The use of tretinoin may be limited by its tendency to cause irritation that may manifest as erythema, desquamation, burning and pruritus. To overcome tolerability problems with the original formulations such as cream, gel and liquid (concentrations of 0.01–0.1%), tretinoin has been reformulated. New preparations such as tretinoin trapped within copolymer microspheres or prepolyolprepolymer-2 gradually releasing the active ingredient over time have shown similar efficacy with diminished irritancy [19]. In addition, a recent study demonstrated improved efficacy and lessened irritation of topical retinoic acid prepared as a cyclodextrin β-complex in hydrogel or moisturizing base (0.025%) compared to a commercial RA gel (0.05%) [56].

Another benefit of the topical retinoids is their ability to reduce postinflammatory hyperpigmentation. A study designed to evaluate the efficacy of topical tretinoin cream in the treatment of hyperpigmented lesions associated with photodamage revealed that patients using all-trans retinoic acid had significant improvement of hyperpigmented lesions compared to patients treated with vehicle [16, 22]. Several mechanisms of action of retinoids on melanocytes have been evaluated in animal and human studies. Treatment of pigment macules resembling human freckles on faces of macaques with topical 0.1% RA has shown to induce significant depigmentation. Morphologic studies revealed an increase of S-phase basal cells, suggesting a dispersion of melanin granules in the acanthotic keratinocytes [23]. A suppressing effect of RA on melanogenesis was not observed in pigmented skin equivalents and monolayer culture of murine and human melanocytes, although hydroquinone showed strong inhibition of melanogenesis. The role of RA in bleaching treatments appears therefore to be in other specific actions, such as promotion of keratinocytes proliferation and acceleration of epidermal turnover [24]. In addition, recent in vivo studies showed that retinoic acid synergistically enhances the melanocytotoxic and depigmenting effects of monobenzylether of hydroquinone in black guinea pig skin [25].

1.8.4.2 Isotretinoin

Isotretinoin is the only drug currently available that influences all four factors that drive the pathogenesis
of acne: (1) sebum production; (2) abnormal follicular keratinization; (3) microbial colonization and (4) inflammation. According to the Committee for Proprietary Medicinal Products (CPMP) of the European Agency for Evaluation of Medicinal Products (EMEA), exclusively severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy should benefit from a systemic treatment with oral isotretinoin [57]. The initial therapy in adults should start at a dosage of 0.5 mg/kg daily followed by dosage adjustments during therapy to avoid dose-related adverse effects and to optimize the therapeutic response of the patient [26, 27]. Serum lipids should be checked before treatment, 1 month after the start of treatment and subsequently at 3 month intervals unless more frequent monitoring is clinically indicated. In addition to current recommendations, female patients of child-bearing potential should use two complementary forms of contraception including a barrier method.

In addition, according to the decisions of the CPMP, isotretinoin should no longer be indicated for treatment of prepubertal acne and should not be recommended in patients younger than 12 years of age [26, 27]. Depending on country and indication differences in recommendations should be considered.

1.8.4.3 Alitretinoin

Alitretinoin (9-cis-retinoic acid) is a FDA-approved topical preparation for treating Kaposi’s sarcoma. Alitretinoin is a naturally occurring endogenous retinoid that binds to and activates all known nuclear retinoic acid receptor subtypes (RAR-α, β and γ) and retinoid X receptor subtypes (RXR-α, β and γ). A recent study evaluated the safety and efficacy of topical alitretinoin gel 0.1% in the treatment of photodamaged skin. According to the authors, treatment was well tolerated by 20 participants and subjectively showed improvement of benign skin lesions such as seborrheic keratoses and precancerous lesions (e.g., actinic keratoses). But larger, blinded and controlled trials are needed to investigate the role of this novel retinoid in the treatment of photoaging [28, 29].

1.8.4.4 Acitretin and Etretinate

Absorption of orally administered acitretin from the gastrointestinal tract is highly variable and is optimized when ingested with food. The mean plasma half-life of acitretin is about 2 days, whereas the mean half-life of etretinate, the ethyl ester of acitretin, is 120 days. In fact, etretinate is detectable in adipose tissue for 18 months or longer. In clinical practice this retinoid has been replaced by acitretin, although there is a risk of re-esterification of acitretin to etretinate in patients who ingest ethanol. Women of childbearing potential who have been treated with acitretin must continue using contraception for 3 years in view of its teratogenic effects [8].

Drug–drug interactions of the retinoids may be relevant, especially interactions with drugs that interfere with cytochrome p450 metabolism, such as cyclosporine or drugs that compete for plasma protein binding such as phenytoin. Besides teratogenicity, mucocutaneous side effects as well as hyperlipidemia, skeletal- and hepatotoxicity, neurological and psychiatric complications have been described during oral treatment with acitretin.

Studies on nuclear retinoic acid receptors have shown that acitretin activates all 3 receptor subtypes (RAR-α, β and γ) without measurable receptor binding; this paradox remains unexplained [30]. The therapeutic efficacy of acitretin is highly dose-dependent: In patients with chronic plaque psoriasis 0.5 mg/kg/day is the recommended initial dose that can be adjusted as needed to enhance efficacy or minimize side effects. Recent multicenter pivotal trials of subjects with severe psoriasis requiring systemic therapy have shown low-dose therapy (25 mg/day) to be an effective strategy for substantially reducing acitretin-associated adverse effects. Many adverse effects associated with acitretin therapy are dose-dependent and can limit the usefulness of this potentially beneficial therapy [31]. In patients with pustular psoriasis, a higher initial dose (1 mg/kg/day) is recommended, whereas in patients with erythrodermic psoriasis a lower initial dose (0.25 mg/kg/day) is advisable. In patients with pustular or erythrodermic psoriasis, monotherapy with acitretin is often highly effective; however combination with other agents is usually recommended for patients with chronic plaque psoriasis [8]. Combination with UVB, psoralen plus ultraviolet A (PUVA) or topical calcipotriol enhances efficacy.
1.8 Retinoid Pharmacology

and limits treatment frequency, duration and cumulative doses [8]. Combination therapy using acitretin and the new biologics has not been studied as yet. [59]

1.8.4.5 Adapalene

Adapalene, a derivative of naphthoic acid, has comedolytic, antiproliferative, and anti-inflammatory properties [32]. Adapalene possesses the biological properties of tretinoin, but has a distinct physiochemical profile, including high lipophilicity and increased chemical and photostability. It exhibits selective affinity for nuclear retinoic acid receptors (RAR-β and RAR-γ) and does not bind to cytosolic retinoic acid binding proteins [33, 34]. Accordingly, numerous clinical trials have compared adapalene and tretinoin in the management of acne vulgaris and concluded that tretinoin 0.05% gel exhibits at least comparable efficacy than adapalene 0.1% gel, but has higher skin irritation potential [35]. Adapalene gel 0.3% is superior to adapalene gel 0.1% in the treatment of moderate to moderately severe acne while retaining a similar safety and tolerability profile [36]. In a 12-week study, the efficacy and safety of the combination of adapalene gel 0.1% with doxycycline (once daily) was compared with doxycycline alone (once daily) for the treatment of severe acne. At Week 12, the combination adapalene-doxycycline was significantly superior to doxycycline alone for change from baseline in total, inflammatory, and noninflammatory lesions. Significant differences in total lesions were observed as early as week 4 [37]. A further study compared efficacy of topical adapalene gel (0.1%) and topical metronidazole gel (0.75%) in the treatment of patients with papulopustular rosacea and revealed significant reductions in the total number of inflammatory lesions in the adapalene group compared with the metronidazole group. There was no significant difference in the scores of erythema and telangiectasia in the adapalene group [38].

1.8.4.6 Tazarotene

Tazarotene is the first topical retinoid developed for the treatment of psoriasis. In two multicenter, double-blind, randomized studies of 6- and 8-week duration, vehicle gel or 0.01% and 0.05% tazarotene gel were administered twice daily to 45 patients with mild to moderate psoriatic plaques, or 0.05% and 0.1% tazarotene gel either once or twice daily to 108 patients with similar symptoms. The 0.01% tazarotene gel showed minimal efficacy. Applications of 0.05% and 0.1% tazarotene gels administered once or twice daily resulted in significant improvements in plaque elevation, scaling, erythema, and overall clinical severity as early as 1 week. Treatment success rates, defined as >75% improvement from baseline, were 45% with 0.05% tazarotene gel vs. 13% with vehicle gel after 6 weeks of treatment and ranged from 48 to 63% with the various tazarotene treatment regimens after 8 weeks of treatment. These improvements were evident at the 8-week follow-up. Treatment-related adverse effects were generally limited to mild or moderate topical irritation and were less frequent with the treatment regimen administered once daily [42].

Combination of topical tazarotene with narrowband ultraviolet B (311 nm) in patients with stable plaque psoriasis reduced the PASI scores more significantly than single narrow-band UVB phototherapy [43]. In addition, tazarotene gel 0.1% has been shown to
improve the therapeutic result of PUVA therapy in patients with chronic plaque-type psoriasis [44]. If the combination of tazarotene with narrow-band UVB or PUVA phototherapy leads to a safer, more effective and faster clearing of psoriasis, compared monotherapy has to be proven in further studies.

1.8.4.7 Bexarotene

Bexarotene is a retinoid X receptor-selective agent that binds to RXR-α and RXR-γ. It can inhibit growth of tumor cell lines of hematopoetic and squamous cell origin and promotes apoptosis [8]. Bexarotene has proven effective in treating all stages of CTCL including those with refractory early-stage disease and advanced-stage disease [45].

In a recent study, effects of bexarotene on malignant T cells isolated from the peripheral blood of patients with the leukemic variant of cutaneous T-cell lymphoma were determined in peripheral blood mononuclear cells (PBMC) from nine patients with Sezary syndrome and a high burden of circulating malignant T cells and six healthy volunteers. Bexarotene produced dose-dependent apoptosis of peripheral blood T cells from patients with Sezary syndrome. The T cells from approximately two thirds of patients were consistently sensitive to bexarotene, whereas those from the remaining one third of patients were consistently resistant to the apoptotic effects of bexarotene. Bexarotene inhibited mitogen-induced interleukin 4 production by the PBMC of patients with Sezary syndrome, and this effect correlated with sensitivity of patients’ cells to apoptosis. In contrast to the retinoic acid receptor-specific retinoid, all-trans retinoic acid, bexarotene does not induce the augmentation of IFN-γ production [46].

In a further study, immunohistochemical parameters for proliferation, differentiation, inflammation, and apoptosis were investigated in a group of bexarotene-treated psoriatic patients. Twenty-nine patients with plaque-type psoriasis were treated for 12 weeks with oral bexarotene in four dose-defined treatment panels. Treatment was initiated in the following consecutive order: 1.0 mg/kg/day, 2.0 mg/kg/day, 0.5 mg/kg/day, and 3.0 mg/kg/day. Immunohistochemical analysis of biopsies taken at the baseline and after 12 weeks of treatment showed significant reductions in Ki-67, keratin 16, transglutaminase, dermal CD4, epidermal CD8, and inflammation scores were seen after bexarotene treatment in combination with a significant increase in keratin 10. No induction of keratin 13 and 19 and no alterations in apoptosis associated p53 expression were observed. These effects of oral bexarotene on proliferation, differentiation, and inflammation parameters have to be confirmed in a larger number of patients to reveal the role of RXR-signaling in retinoid-associated keratin expression and in treatment of psoriasis patients [47].

Hypertriglyceridaemia of all grades was recorded in 79% of patients, who took oral bexarotene in the study in early-stage CTCL, hypercholesterolaemia occurred in 48% of patients and hypothyroidism in 40% [48]. A recent publication of an expert commission suggested a strategy which anticipates that these common adverse events are likely to occur and recommends the early use of preventive therapy to lower triglycerides and elevate thyroid hormone levels in the blood, followed by subsequent monitoring, dose adjustment during bexarotene treatment, and titration of the daily bexarotene dose from 150 to 300 mg/m², which is optimal for most patients [49].

1.8.5 Experimental Approaches

Tazarotene is a retinoid that has also been studied for its effects in treating and/or preventing skin cancer [51]. Treatment of basal cell carcinomas and squamous cell carcinomas in situ with topically applied tazarotene 0.1% gel has been reported [21, 51, 52]. In these studies tazarotene was effective in curing some superficial and nodular BCCs as well as squamous cell carcinoma in situ showing complete remission in approximately 30–50% of treated lesions. Additional studies are needed to confirm the safety and efficacy of tazarotene as a topical anti-cancer agent.

To modulate or raise the levels of endogenous retinoic acids several “retinoic acid metabolism-blocking agents” (RAMBAs) have been developed that inhibit cytochrome p450 dependent metabolism especially of all-trans retinoic acid. The only RAMBA that is approved by the FDA for this indication is liarazole, an imidazole derivative which inhibits 4-hydroxylation of retinoic acid, thereby increasing tissue levels of retinoic acid. In the US, orally administered liarazole is approved for the treatment of
congenital ichthyosis as an orphan drug. In a double-blind comparative trial of liarozole vs. acitretin, 32 patients with X-linked recessive ichthyosis, lamellar ichthyosis and bullous congenital ichthyosiform erythroderma were randomized to be treated with either oral liarozole 75 mg in the morning and 75 mg in the evening or with acitretin 10 mg in the morning and 25 mg in the evening for 12 weeks. Between-group comparisons for efficacy and tolerability revealed no major statistically significant differences. Based on the overall evaluation of the response to treatment at endpoint, 10 of 15 patients in the liarozole group and 13 of 16 patients in the acitretin group were considered by the investigator to be at least markedly improved. The expected retinoic acid-related adverse events were mostly mild to moderate and tended to occur less frequently in the liarozole group. These study results may indicate that liarozole at a daily dose of 150 mg is equally effective as a treatment for ichthyosis as acitretin but shows a trend towards a more favorable tolerability profile [53].

1.8.6 Complication to Avoid

Systemic retinoids are highly teratogenic and up to the present time it has not been possible to separate this undesirable toxicity from their therapeutic effects [8]. Percutaneous absorption of topically applied retinoids is minimal; indeed in a recent study two groups of 14 female volunteers of child-bearing age were kept on a Vitamin A-poor diet and treated topically for 21 days with creams containing 0.30% retinol or 0.55% retinyl palmitate on approximately 3,000 cm² of their body surface area, amounting to a total of approximately 30,000 IU Vitamin A/subject/day. With the exception of transient mild to moderate topical irritation on the treatment sites, no adverse topical or systemic effects were noted. On days 1 or 21 of topical treatment, no changes were measured in individual or group mean plasma Cmax, AUC 0–24 h or other pharmacokinetic parameters of retinol, retinyl esters or retinoic acids relative to prestudy data [54].

Although studies have shown that topically applied tretinoin in the first-trimester of pregnancy was not associated with any adverse outcome, it is impossible to exclude the possibility that some women/infants may be uniquely susceptible to even trace amounts of retinoids; it is essential to avoid using topical retinoids altogether during pregnancy [55]. In the US, the oral but also the topical form of tazarotene are rated as “pregnancy category X” and are contraindicated for women who are or may become pregnant [29].

1.8.7 Global Variations

Global variations have been reported for the prevalence of diseases frequently treated with topical or oral retinoids such as acne vulgaris. Furthermore due to country specific approval authorities, differences in the approval of a retinoid for application in specific diseases, as well as differences in contraindications, patient information or consent are known. For example topical formulations of tazarotene for the treatment of acne vulgaris are only available in the US and few other countries [19]. Because of the several known side-effects, country-specific approvals and recommendations have to be consulted before applying retinoid containing drugs.

References

27. The European Agency for the Evaluation of Medicinal Products. Committee for Proprietary Medicinal Products. Summary information on a referral opinion following an arbitration pursuant to article 29 of Directive 2001/83/EC for isotretinoin. CPMP/8211/03, 17 October 2003
35. Ioannides D, Rigopoulos D, Katsambas A (2002) Topical adapalene gel 0.1% vs. isotretinoin gel 0.05% in the treatment of acne vulgaris: a randomized open-label clinical trial. Br J Dermatol 147(3):523–527
1.9.1 UVB phototherapy

<table>
<thead>
<tr>
<th>Key Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narrow-band UVB was developed based on the phototherapy action spectrum</td>
</tr>
<tr>
<td>Mechanisms of action: induction of apoptosis and immune suppression</td>
</tr>
<tr>
<td>Improved targeting achieved using 308-nm excimer light/laser phototherapy</td>
</tr>
<tr>
<td>Low risk of photocarcinogenesis</td>
</tr>
</tbody>
</table>

1.9.2 Mechanisms of Action of Ultraviolet Phototherapy

Ultraviolet (UV) phototherapies using broad-band UVB (290–320 nm) and narrow-band UVB (311–313 nm) are established treatment modalities for refractory skin diseases such as psoriasis, atopic dermatitis (AD), vitiligo, and eczema [1]. Although the mechanisms involved in the successful treatment of these refractory skin diseases remain unclear, the effectiveness of these phototherapies is considered to be dependent on their respective action spectra. Previous studies indicate that the mechanisms of action underlying these phototherapies are mainly related to the induction of apoptosis in pathogenetically relevant cells and antigen-specific immunosuppression [2].

1.9.2.1 Action Spectrum of UVB Phototherapy

In 1980, the action spectrum of UV phototherapy for treating psoriasis was examined using a monochromator to produce radiation between 254 and 313 nm [3]. Shorter wavelengths (254, 280, and 290) were not phototherapeutic for psoriasis. Longer wavelengths (296, 300, and 304 nm), however, were effective in inducing the erythema reactions needed to clear psoriasis, with subcrythemogenic exposure of 313 nm resulting in complete clearing in all subjects. This study suggested that wavelengths greater than 296 nm may be a more effective phototherapy for psoriasis. This observation led to the successful development of narrow-band UVB for clinically effective treatment of psoriasis [1].

1.9.2.2 The Mechanisms of Action of UVB Phototherapy: Apoptosis and Immune Suppression

Within the UVB spectrum (290–320 nm), narrow-band UVB (311 nm) phototherapy has grown in popularity for irradiating refractory lesions such as AD, psoriasis, and vitiligo [1]. In addition to its efficacy in treating mild and moderate stages of AD, narrow-band...
UVB is particularly effective for treating psoriasis, resulting in faster clearance of lesions, fewer episodes of excessive erythema, and a longer remission [4]. For psoriasis, the efficacy of narrow-band UVB (311–313 nm) as compared to broad-band UVB (290–320 nm) irradiation is attributable to the ability of 311 nm narrow-band UVB to deplete skin-infiltrating T cells more effectively from the epidermis and dermis of psoriatic plaques [5]. There are two modes of action of narrow-band UVB: induction of apoptosis and induction of antigen-specific immunosuppression [5, 6]. The narrow-band UVB-induced depletion of pathogenetically relevant T cells is due to the induction of apoptosis [5].

Narrow-band UVB therapy generally induces a relatively long remission period of approximately 4–6 months in patients with psoriasis. Thus, the induction of apoptosis might be only partially responsible for this relatively long remission period. The role of regulatory T cells (Treg) should also be considered as narrow-band UVB radiation induces local and systemic immune suppression in a model of contact hypersensitivity [6].

Evidence suggests that regulatory T cells have an immune regulatory function and a key role in peripheral tolerance [7, 8]. The peripheral T cells from patients receiving UVB phototherapy exhibit a CD4+CD25+ T cell profile [9]. The induction of Treg cells following UV irradiation is associated with UV-induced DNA damage. UV-induced DNA damage induces Langerhans cells to move from the skin into the draining lymph nodes, and interleukin-12 can induce DNA repair and limit the number of UV-damaged Langerhans cells in the draining lymph nodes [10]. It is thus possible that UV-induced DNA damage alters cutaneous antigen-presenting cells and enhances their ability to activate Treg cells. UV irradiation increases the proportion of fluorescein isothiocyanate-bearing dendritic cells within the draining lymph nodes [11] that exhibit deficient maturation and deficient Th1 T cell priming [12]. UV Irradiation, however, also promotes the generation of CD4+CD25+Foxp3+ T cells within the draining lymph nodes following immunization [13]. Among these CD4+CD25+Foxp3+ T cells are cells with an antigen-specific regulatory function in vivo [14]. The findings from these experiments suggest that CD4+CD25+Foxp3+ T cells, the so-called Treg, are responsible for the immunosuppressive effect.

1.9.2.3 Clinical Efficacy of Narrow-Band UVB for Psoriasis and Atopic Dermatitis

In a previous bilateral comparison study of 23 patients treated for psoriasis with narrow-band UVB (311–313 nm) and broad-band UVB (290–320 nm), narrow-band UVB (311–313 nm) cleared psoriatic plaques more effectively than broad-band UVB (290–320 nm) [15]. Narrow-band UVB (311–313 nm) also produced a more potent apoptosis-inducing action than broad-band UVB (290–320 nm). The in vitro T cell apoptosis-inducing capacity of narrow-band UVB (311–313 nm) appears to parallel its clinical efficacy [15].

Narrow-band UVB is also used to treat other refractory skin dermatoses. An open study of air-conditioned narrow-band UVB demonstrated superior effectiveness compared to conventional UVB, broad-band UVA, and low-dose UVA I therapy in treating chronic severe AD [16, 17]. The therapeutic effectiveness of narrow-band 311 nm UVB therapy for chronic, moderate AD was first shown in an open trial conducted by George et al [16]. Patients were monitored for severity of clinical Symptoms as well as glucocorticoid use 12 weeks prior to phototherapy, during the 12 weeks of phototherapy, and for another 24 weeks after the cessation of phototherapy. Narrow-band UVB (311 nm) decreased the clinical severity as well as significantly reduced the use of glucocorticoids. The majority of patients still exhibited these beneficial effects 6 months after cessation of narrow-band (311 nm) therapy.

1.9.2.4 Excimer Light/Laser

Another option for phototherapy, and treatment of psoriasis in particular, is the excimer laser, or light therapy (308 nm). This method can effectively target the affected area (targeting therapy) and prevent unwarranted exposure of normal skin [18, 19]. Moreover, compared to narrow-band UVB, excimer light effectively treats resistant and localized psoriasis lesions with fewer treatments and a lower cumulative UVB dose [19]. In this study, the mean number of treatments using an excimer lamp was approximately one-third of that using narrow-band UVB phototherapy [19].
Although shorter wavelengths may damage DNA and present greater risks of erythema and carcinogenesis, such long-term risks may be outweighed by the comparative advantages of fewer treatments and lower cumulative UVB doses.

### 1.9.3 Complications to Avoid

The photocarcinogenic risks associated with TL-01 UVB (narrow-band UVB) were examined in a study of 1908 patients from the Scottish Cancer Registry with basal cell carcinoma, squamous cell carcinoma, and malignant melanoma [20]. During the median 4-year follow-up, there was no increased incidence of squamous cell carcinoma or malignant melanoma; however, there was a small increase in basal cell carcinoma.

### 1.9.4 Global Variations

Narrow-band UVB is available to dermatologists all over the world. More targeted UVB phototherapy, using the excimer light/laser, was recently introduced in only a limited number of countries.

### 1.9.5 UVA1 Phototherapy

#### Key Features

- Effective for the treatment of T cell or mast cell-mediated diseases and fibrous or connective-tissue diseases.

#### Take Home Message

- Narrow-band UVB is becoming a popular modality for the treatment of refractory skin diseases such as psoriasis, AD, vitiligo, and eczema. Based on the underlying mechanisms of UVB phototherapy, three steps of irradiation techniques, i.e., whole body irradiation, partial body irradiation and targeted phototherapy can be recommended particularly for the treatment of psoriasis (Fig. 1.9.1).

#### Mechanism of Action of Ultraviolet A-1 (UVA1) Phototherapy

The longer wavelengths of ultraviolet (UV) A1 phototherapy (340–400 nm), which penetrates the dermal layers more deeply than shorter wavelength UVB radiation (290–320 nm), clear lesions in the treatment of AD by inducing apoptosis in skin-infiltrating T helper cells [21], which may be associated with downregulation of the in situ expression of T helper cell-derived cytokines as well as a depletion of intradermal CD4+ cells. In vitro, the induction of T helper cell apoptosis is mediated through activation of the FAS/FAS-ligand system in irradiated cells as a consequence of singlet oxygen generation. Generation of singlet oxygen is considered to have a central role in inducing apoptosis and is an underlying mechanism of UVA1 phototherapy [21].

#### Clinical Efficacy

##### 1.9.7.1 Atopic Dermatitis

UVA1 was first used to treat patients with AD. The therapeutic effectiveness of UVA1 therapy was evaluated in...
an open study in patients with acute, severe exacerbations of AD. UVA 1 was highly effective in quickly inducing clinical improvement and reducing elevated serum eosinophil cationic protein in patients exposed to 130 J/cm² UVA1 daily for 15 consecutive days [22].

Although there has been some success in treating mild and moderate AD with broad-band UVB, combined UVA/UVB, broad-band UVA, low-dose UVA1, and narrow-band UVB (311 nm) as monotherapies [23], these forms are also used in combination with topical glucocorticoids to reduce the amount of glucocorticoid required. Most of these forms of UV therapy should be used to induce long-term improvements and are considered relatively safe, even when used over extended periods. The exception is UVA 1, which is considered a more potent and aggressive modality that should be used only as a monotherapy. UVA 1 is dose-dependent and medium-dose and high-dose UVA 1 is effective for treating acute exacerbations of AD [23].

1.9.7.2 Localized and Systemic Scleroderma

UV A1 (340–400 nm) is also an effective treatment for morphea (localized scleroderma), which is a disorder characterized by the overproduction of collagen by fibroblasts in affected tissues leading to thickening of the dermis and subcutaneous tissues. Patients with morphea have increased levels of circulating intercellular adhesion molecule-1 and fibrogenic T-helper 2 cytokines, such as interleukin 4 and transforming growth factor-beta (TGF-β). These cytokines recruit eosinophils and other inflammatory cells and induce fibroblasts to synthesize excessive collagen and connective-tissue growth factor. UV A1 irradiation disturbs cellular responsiveness to TGF-β1 through the induction of non-functional latent TGF-β and the downregulation of TGF-β receptors, which is a possible mechanism underlying the efficacy of UVA 1 treatment [24].

Treatment of systemic sclerosis using UVA 1 phototherapy (340–400 nm) has recently become accepted. Direct irradiation of the skin with UV rays activates matrix metalloproteinase, reduces the types of cytokines involving T cells, and inhibits T cell activation [25]. UVA 1 depletes skin infiltrating T cells through the induction of T cell apoptosis and upregulation of the expression of matrix metalloproteinase-1 (collagenase-1) in dermal fibroblasts [26]. This finding led to the idea that UVA 1 might be beneficial for the treatment of systemic sclerosis.

The mechanisms involved in the ultramicroscopic changes underlying the UVA 1 therapy-induced clinical softening of collagen fibrils were studied by comparing the diameters of the collagen fibrils [27]. The presence of an inflammatory infiltrate consisting of T helper cells and a dysregulated matrix metabolism leading to excessive deposition of collagen are two pathogenetic factors responsible for the development of fibrosis and sclerosis in patients with systemic sclerosis [28]. The ultrastructure of cutaneous alterations occurring in clinically softened skin was also compared. The findings indicated that the direct action of UV light on the collagen fibrils and fibroblasts induced a decrease in the size of the broad collagen fibrils, and the equalization of the thickness and appearance of thin fibrils are considered to be related to the degradation and synthesis of collagen. The degradation and synthesis of collagen may be the underlying mechanism. This is consistent with the findings of another recent study suggesting that radiation stimulates collagenase synthesis in fibroblasts, resulting in collagen degradation and de novo synthesis of type I collagen [29].

1.9.8 Complications to Avoid

UVA1 phototherapy has not been evaluated for long-term risks. This light source should be used with caution, although high efficacy is expected for AD and scleroderma.

Take Home Message

- UVA1 phototherapy effectively treats AD by inducing pathogenetically relevant CD4+ cells.

1.9.9 Global Variations

UVA1 phototherapy is only available in a limited number of countries.
References


uter ultraviolet B light (narrow-band UVB) induces apopto-
immunol Photomed 24:32–37


ctic cell migration. Immunology 77:394–399


cutaneous immunization through ultraviolet-irradiated skin is transferable through CD4+CD25+ T regulatory cells and is dependent on host-derived IL-10. J Immunol 176: 2635–2644


20. Man I, Crombie IK, Dawe RS et al (2005) The photocarcino-


beta in the age-related alterations induced by ultraviolet A Irradiation. J Invest Dermatol 120:703–705
25. Herrmann G, Wlaschek M, Lange TS et al (1993) UVA Irradiation stimulates the synthesis of various matrix metal-
loproteinases (MMPs). Exp Dermatol 2:92–97
26. Yin L, Yamauchi R, Tsuji T, Krutmann J, Morita A (2003) The expression of matrixmetalloproteinase-1 mRNA induced by ultraviolet AI (340–400nm) is phototherapy relevant to the glutathione (GAH) content in skin fibroblasts of sys-
Lasers and laser technology has transformed noninvasive cosmetic dermatology.

Any understanding of laser physics leads to better treatment results and a lesser incidence of complications.

A variety of lasers and laser-like approach are now used to treat vascular lesions, pigmented lesions, unwanted hair and a variety of age related cutaneous changes.

Photodynamic therapy represents the use of a topical photosensitizer in conjunction with a laser or light source to treat various signs of photodamage.

### 1.10.1 Background

The history of lasers can be traced back to the nineteenth and twentieth centuries. Albert Einstein in 1917 first coined the term stimulated emission as it applies to today’s lasers. Laser-induced stimulated emission begins with an atom with an electron in an excited state occupying a high orbit. If this electron was to spontaneously decay to a lower energy orbit, it would elaborate a photon of characteristic energy as described above. If this electron (while still excited) is targeted by a photon matching the photon that would be elaborated spontaneously, it will result in the ejection of two photons, the incoming one and a forcible expulsion of the photon from the excited electron with a return of this electron to its resting state.

What followed in the 1960s was an explosion in the literature of descriptions of many of the lasers that we currently employ. In 1961, Javan described the Helium Neon laser (He-Ne) and within the next few years Q-Switched lasers and the Neodymium YAG (Nd:YAG), argon, the carbon dioxide and the pulsed dye laser were described. Selective photothermolysis, a concept first described in 1980s revolutionized our understanding of today’s laser and light source dermatology.

Photodynamic therapy (PDT), a later evolution of laser and light-based technology, is a noninvasive technique used in the treatment of various skin disorders. Used initially for the treatment of cutaneous tumors, its objective is to use laser or light-based technology in conjunction with a photoactivating substance to cause selective destruction of the desired target tissue without causing damage to other normal surrounding structures. In dermatology, its application includes precancerous lesions such as actinic keratoses and Bowen’s disease, malignant conditions including basal cell carcinoma and squamous cell carcinoma, as well as benign inflammatory processes such as psoriasis and acne vulgaris. PDT has become an increasingly safe and effective treatment modality.

PDT was first introduced in the early 1990s as an experimental treatment which consisted of oxygen, light and a photosensitizing agent to cause tumor cell death.
destruction [3]. However, it was not until 1990, when Kennedy and colleagues introduced the use of 5-aminolevulinic acid (5-ALA) that PDT as we know of it had its dramatic impact on dermatology [4]. 5-ALA became a potent topical photosensitizing agent that could be used for PDT without significant phototoxicity. This agent was approved by the US FDA in 1999 in combination with light for the treatment of actinic keratoses [5]. Since then, the field of PDT has generated vast interest in terms of research and clinical application. In Europe, PDT is being used for actinic keratoses and basal cell carcinomas [6,7]. Off-label uses, in both the US and Europe, include Bowen’s disease, cutaneous T-cell lymphoma, psoriasis, acne, and most recently, photorejuvenation and hair removal [8–10].

1.10.2 Characteristics

Laser light is different from ambient light in that it is coherent, collimated, monochromatic and can be pulsed.

*Spatial and temporal coherence:* The light waves in laser light are “in step,” traveling in exactly the same direction with very little beam divergence.

*Collimation:* This refers to a laser beam’s ability to retain its intensity over a long distance with low diffusion of light compared with a torch or other light source. These two factors allow a laser beam to be tightly focused to a point of maximum energy as necessary. This point may be used to cut tissue or just be a maximum point of energy for high-energy interaction with a target in the tissue termed as chromophore.

*Monochromicity:* The third important characteristic of lasers is that the light is of the same single wavelength, that is, it is monochromatic. This allows the laser to interact with certain structures in the skin that are able to absorb that wavelength better than its neighboring structures.

*Pulsing:* The fourth characteristic of laser beams is their ability to be pulsed. Although occasionally lasers are used in continuous mode most are used in a pulsed fashion. This allows the pulse to impact the target in tissue just long enough to damage it without damaging surrounding structures to any degree. The duration of pulse required is proportional to the size of the target.

Nonlaser, intense pulsed light (IPL) makes use of an incoherent high output flashlamp to produce a multiwavelength output. IPL technology makes use of the additive effects of bands of wavelengths rather than a single wavelength to exert a tissue effect. It thus does not rely on monochromicity, collimation or spatial and temporal coherence and cannot be focused but simply adds the effect of a little light in each of many wavelengths to exert a powerful absorption by the target-absorbing chromophore. This technology relies on the fact that chromophores in the skin absorb energy over a broad spectrum of light wavelengths and do not have to be targeted by just the most highly absorbed peak of that absorptive band.

The uses of lasers in dermatology span the visible light lasers from about 300 nm through to the mid-infrared. These wavelengths are able to locate specific chromophores or targets in the skin. Endogenous targets in the skin include hemoglobin (oxygenated and deoxygenated), melanin, and water. Sometimes exogenous chemicals may find their way into the skin such as implanted tattoos or other foreign materials allowing us another target. At other times we may add or augment an existing target to the skin by applying, implanting or ingesting a sensitizing material to an area and then shining light or laser as is done with PDT.

The most common mechanism that is used by lasers is selective photothermolysis inducing thermal injury, denaturing and coagulating target cells. The concept of selective photothermolysis stresses on selective absorption by colored targets such as blood vessels and pigmented cells of appropriately pulsed laser light. This tenet has revolutionized the safety and efficacy of laser therapy, ensuring that thermal injury is specifically confined to the intended target leaving the rest of the skin relatively unaffected.

Another mechanism of laser interaction also involves heating of tissues but in a slightly different way. When a laser has water as its prime target, the beam becomes relatively nonselective as all skin contains this chromophore. However, the laser may be made capable of limiting the damage to the intended target. The laser is designed to produce a high-energy short-duration pulse capable of superheating the water in the cells, vaporizing this water and producing a smoke or plume containing steam and cellular contents. If the energy, pulse duration and choice of laser are appropriate, relatively little thermal injury is left in tissue. In this way, 000 selectivity of ablation occurs and unintended targets are spared. Ablation as a form
A third mechanism of interaction is photochemical interaction. Photochemistry exists all around us with photosynthesis in plants, UV photo chemotherapy for the treatment of psoriasis and eczema, some photosensitive skin disorders, vitamin D production and the act of vision being examples. The excimer laser (308 nm) used in the treatment of hypopigmented disorders and psoriasis cutaneous T cell lymphoma, atopic dermatitis and many other dermatologic disease states is an example of a photochemical reaction inducing apoptosis of target cells including T lymphocytes. As described above, PDT is the use of a long wavelength deeply penetrating laser or light to activate porphyrin labeled tissues such as skin cancers and precancerous lesions or shorter wavelengths to target more superficial diseases.

Currently, there are two topical agents that are widely used as photosensitizing drugs for PDT. These are aminolevulinic acid and methyl aminolevulinic acid [11–13]. These agents stimulate the production of porphyrins which act as powerful photosensitizers.

### 1.10.3 Aminolevulinic Acid

5-ALA is an endogenous sensitizer and a metabolite of heme biosynthesis. It is the first approved photosensitizing agent and the most commonly used drug for PDT. Various clinical trials have proven its benefit as a photosensitizer in the PDT of actinic keratoses, basal cell carcinoma, and Bowen’s disease. Its main limitation is its poor penetration into the skin because of its hydrophilic and charge characteristics. The use of different enhancers of PpIX production, as well as the development of new drug delivery systems, and the modification of its molecule have improved its penetration.

The use of dimethylsulphoxide (DMSO) as a vehicle improves skin penetration of ALA and leads to higher porphyrin accumulation in tumor tissue. Addition of topical glycolic acid also has been shown to enhance ALA’s penetration in tissue. One study evaluated the effectiveness of the use of a water-soluble adhesive patch for drug delivery, while another concluded that elevating the skin temperature during topical ALA application can induce greater penetration, thus improving treatment results. A recently proposed concept to enhance the efficacy of PDT, especially in the treatment of thicker lesions, is through the use of intraliesional ALA.

#### 1.10.3.1 Methyl Ethyl Aminolevulinic Acid

Methyl 5 aminolevulinate (MAL) is an ester derivative of 5 amino levulinic acid. It is more lipohilic when compared to ALA and has been approved by the US FDA solely for the management of actinic keratoses. MAL has been registered in Europe, Australia and New Zealand for the treatment of actinic keratoses and superficial and nodular basal cell carcinoma. MAL leads to high penetration in tumor cells (high ratio of porphyrin fluorescence depth to tumor depth) with less fluorescence in adjacent normal tissues and acceptable cosmetic results. Clinical trials have proven its efficacy for both actinic keratoses and basal cell carcinoma.

The absorption spectra of these current sensitizing agents are in the range of 600–700 nm, which limits its use to superficial tumors since light penetration at these wavelengths is only up to 3 mm.

Finally, photomodulation is a totally different process which attempts to make use of non thermal light tissue interactions usually by banks of narrow band light emitting diodes. This is presumed to work at cellular and sub cellular level to change the regulation of protein synthesis [14]. Light-emitting diodes (LED) emit low-intensity light ranging from UV to visible to infrared. LED devices may be arranged in quite large panels so that large surface areas can be treated.

### 1.10.4 General Therapeutic Outline

#### 1.10.4.1 Ablative Technologies

#### 1.10.4.1.1 Carbon Dioxide (CO₂) Lasers

The advent of high-energy short pulse CO₂ lasers and scanning technologies provided the first safe reproducible laser therapies for facial rejuvenation. Various studies have documented a relatively
successful technique with a satisfactory complication profile [15–19].

The CO₂ laser operates in the far-infrared wavelength (10,600 nm) and is absorbed by water. The laser will thus ablate all tissue in its path to an even depth. Energy at this wavelength is rapidly absorbed and dissipated in a very short distance of tissue.

Many advances have been made in the use of CO₂ lasers for treating the surface of the skin (skin resurfacing). Technology has decreased the dependence on the skill of the operator thus improving reproducibility of results. Carbon dioxide lasers are able to ablate relatively thin layer (20–50 μm) due to rapid extinction of the beam in tissue. For successful char free laser therapy a system must deliver enough energy to vaporize tissue (5 J/cm²) in a time shorter than the thermal relaxation time of the skin (1 ms).

1.10.4.1.2 Erbium:YAG Laser

Despite the quite impressive advances represented by the CO₂ laser, inherent problems of this laser system were apparent. These include their somewhat delayed healing due to a protracted inflammatory or “lag” phase. This phase describes the removal of heat damage in the base of the wound before the phase of re-epithelialization. Although much improved over previous older laser systems, the newer CO₂ lasers still left some necrotic thermally damaged tissues at the base of the wound that must be removed before epidermal regrowth can ensue. There were also reports of delayed appearance of alabaster (white) skin some months to years after carbon dioxide laser resurfacing alone.

The erbium laser wavelength is 10 times more avidly taken up by water than the CO₂ wavelength leading to more complete ablation of tissue producing only a very fine layer of thermal damage Most investigators suggest that 4–5 μm of tissue is removed per joule of fluence utilized [20]. With an epidermis between 60 and 100 μm in thickness, somewhere between 15 and 25 joules of energy is thus required for complete epidermal ablation. There is almost a perfectly linear relationship between the energy delivered and the depth of ablation, whether it is in the epidermis or dermis. There is little residual heat damage with this machine, essentially becoming in effect like an ultimately controllable dermabrasion. This makes the erbium laser useful for resurfacing with relatively rapid and predictable healing (Fig. 1.10.1a, b).

It can be used either alone, or with other procedures and in combination with carbon dioxide laser resurfacing.

The erbium laser can also be used for laser resurfacing of photoaged skin or to treat actinic cheilitis, postoperative scars and elevated grafts [21,22]. It can also be effective in the treatment of a variety of epidermal and dermal conditions such as seborrheic keratoses, xanthelasma, and syringomas.

![Fig. 1.10.1](image-url) (a) Photodamaged skin before erbium laser resurfacing. (b) Improvement in photodamaged skin after erbium laser resurfacing
Long-pulse erbium lasers have also been used as a mechanism for providing enhanced hemostasis, allowing a short-pulsed erbium laser to penetrate deeper. This can be useful where depth of penetration is important such as the more severe photodamage patient or in conditions such as rhinophyma.

### 1.10.4.1.3 Plasma Skin Resurfacing

A new technology utilizes a nonlaser device to generate plasma, a cloud of electrons, from nitrogen atoms and a spark of radiofrequency. This energy is transferred into the skin. The epidermis initially is left intact, only later to shed as healing is completed. The resultant effect may be similar to the rejuvenation effect induced by an erbium laser but with perhaps less posttreatment morbidity (Fig. 1.10.2a, b).

---

**Fig. 1.10.2** (a) One day after aggressive plasma resurfacing for photoaged skin, (b) 1 week after aggressive plasma resurfacing. Total re-epithelialization has occurred

---

### 1.10.5 Nonablative Technologies

These technologies may be divided in various ways. A reasonable method of dividing these myriad systems is by the target effected by the lasers.

Colored chromophores are impacted upon predominantly by visible light lasers and light sources. Such systems deliver a variety of wavelengths such as the frequency doubled Nd:YAG, KTP green light 532 nm and pulsed dye yellow light 585–595 nm lasers, broadband flashlamps (IPL, non coherent filtered flashlamp light source), or narrowband LED systems.

A distinctly different category of nonablative technologies include near infrared wavelength emitting lasers and other technologies targeting dermal water. All of these systems provide a general heat injury leading to neocollagenesis (Fig. 1.10.3a, b).

---

**Fig. 1.10.3** (a) Telangiectases before KTP laser treatment, (b) Improvement in telangiectases after laser treatment
Nonablative lasers and light sources that were originally designed for the treatment of vascular and pigmented abnormalities in the skin have also now been adapted successfully in the more general “photorejuvenation” of the patient. Many improvements have been made in the delivery of light energy in areas as diverse as energy delivery, spot size, beam profile, pulsing, and protection of the epidermis, and the advent of noncoherent lamps. Higher powered lasers have allowed for larger treatment spot sizes allowing for facial, chest and neck treatment.

Color is an important independent sign of aging and gives the person somewhat an unkempt appearance. Particular focal signs of photoaging such as telangiectases and pigmented lesions are now particularly well targeted along with the broader problems of diffuse erythema, flushing and dyschromia. Treatment of these problems produces a significant change that is clearly visible and highly satisfying for the patient and the clinician alike.

1.10.5.1 Vascular Lasers and Light Sources

1.10.5.1.1 Appropriate Wavelength

Continuous or quasi-continuous lasers with wavelengths well matched for vascular lesions such as krypton (568 nm), copper vapor (578 nm), argon dye (577 nm) and KTP (532 nm) were introduced in the 1970s and 1980s (Fig. 1.10.4a).

Since then, other wavelengths (530–600 nm) have also been used. Although some use has been made of wavelengths between 800 and 900 nm, most attention to longer wavelength devices has been directed toward 1,064 nm Nd:YAG lasers that are used for the treatment of deeper vascular targets. Of note such wavelengths, between 755 and 1,064 nm, are highly successful for the removal of unwanted hair (Figs. 1.10.4b and 1.10.5a, b).

A recent growing trend has been toward the use of multi wavelength laser machines. Examples include a 532-nm and 1,064 nm laser and a combined 585 and 1,064 nm laser. Some laser manufacturers offer combined lasers and light sources with the base unit acting as the powering source and various handpieces clipping into this base unit. Such systems provide either variously filtered wavelengths for IPL therapy or actual lasers powered by the base light source. One should expect that such multiple wavelength systems will be increasingly used in the future.

1.10.6 Treatment Issues

Many different laser systems are able to adequately treat general facial telangiectases and benign epidermal pigmented lesions. These early lasers, however, were restricted in their ability to treat large areas of the skin. Initially robotized scanners were used so as to allow a...
larger area to be treated in a single treatment session. However, today’s modern lasers rely on large spot sizes and speed to provide adequate area treatment [23].

### 1.10.6.1 Q-switched and Long-Pulsed Laser Systems

Q-Switched lasers are able to deliver pulses of laser light with high-peak powers and nanosecond duration. Using wavelengths that are selectively absorbed by pigment granules (melanosomes), such lasers tend to break up pigment particles. Since the duration of the pulse is so short, heat damage to adjacent tissues is minimized.

The Q-switched frequency doubled Nd:YAG, the Q-switched ruby, and the Q-switched alexandrite lasers are probably equally effective in the treatment of pigmented lesions.

Although Q-switched lasers are the accepted gold standard for dermal melanocytic lesions and tattoos, a recent interest in longer pulsed lasers and light sources (millisecond domain) has resulted in a number of these lasers also being used for both the treatment of superficial pigmented lesions and general dyschromia – two major issues in facial rejuvenation. Frequency doubled KTP:YAG (532 nm), long pulsed dye, and alexandrite (755 nm) lasers are among such lasers successfully utilized for photorejuvenation. IPL may also be preferable to Q-switched lasers for certain darker skin types because use of such light-based systems may lessen the incidence of treatment rebound post inflammatory hyperpigmentation.

### 1.10.6.2 Yellow and Green Light Lasers

The yellow light pulsed dye laser has always been important for the treatment of a variety of vascular malformations. This laser was initially less popular for the treatment of widespread adult vascular ectasia because of the treatment induced purpura that was an obligate accompaniment of earlier laser models that emitted short (0.45 ms) pulse durations. In later models longer pulsing has enabled mostly nonpurpuric treatments. Pulse durations have been extended up to 40 ms for nasal vascular treatment and usually at 6–10 ms for general facial rejuvenation treatment. Such longer pulsed systems have found great utility for the treatment of individual telangiectases, angiomas, general facial erythema and flushing [24].

Flashlamp pumped dye lasers appear to have some ability to increase dermal collagen and thus possibly having an impact on treating some dermal signs of photodamage [25,26]. The laser induced neocollagenesis has been presumed to be an effect of the interaction between the laser and the vasculature inducing the release of inflammatory cytokines and mediators of inflammation. This is then followed by an increase in fibroblastic activity initiating reparative mechanisms including increased collagen formation.

---

**Fig. 1.10.5** (a) Before intense pulsed light treatment of lentigines. (b) Improvement after 1 intense pulsed light treatment
The KTP laser is useful for many rejuvenation purposes [27]. It can be useful for individual lesions including vessels, pigmented lesions, and a variety of unusual applications such as sebaceous hyperplasia, syringomas, and fibrous papules.

1.10.6.3 Nonlaser Light Sources

A chromophore such as hemoglobin in blood vessels or melanin contained within melanocytes has a characteristic spectrum of absorption over a wide range of wavelengths. Absorption is generally better at some wavelengths than at others. Lasers usually focus on a single wavelength at or near a peak on the absorption spectrum. Another, now highly popular, approach has been to use an IPL source to emit small amounts of light over a broadband of wavelengths to interact with the target over the extent of the absorption spectrum. These emitted energies, at all the different wavelengths, when added together equate to a high enough total energy to adequately treat a number of vascular and epidermal manifestations of photodamage [28–32].

It has been suggested by some that current nonlaser light-based systems may eventually become more popular than lasers because of comparative cost advantages, recently enhanced engineering changes, and widespread popularity of such nonlaser light-based systems when used for full facial rejuvenation (Fig. 1.10.6a).

The broad range of wavelengths included in the IPL emission (500–1,200 nm) is curtailed at the lower end (shorter wavelengths) by use of “cut off” filters. The treatment thus allows the emission of green, yellow, red, and infrared wavelengths, at the same time allowing the colored chromophores (hemoglobin and melanin) and water to be simultaneously targeted. This has the theoretical advantage of dealing with all the common problems of photodamage at the same time. The large treatment head allows IPL treatments to be performed expeditiously.

Facial rejuvenation, with a variety of IPL sources, is generally undertaken with a 550–570 nm cutoff filter. Using this approach most aspects of photodamage, such as telangiectasia, dyschromias, dilated pores, skin textural changes, and mild wrinkling can be treated. A variety of IPL sources, made by a variety of manufacturers, are now available.

1.10.6.4 Infrared Lasers and Light Sources

As one moves from the visible to the infrared wavelengths a number of changes occur in the absorption characteristics of the skin. Depth of beam penetration of the laser or light increases as colored chromophores are less specifically targeted; more transmission rather than absorption occurs. Near infrared wavelengths, up to about 1,100 nm, can be absorbed by

Fig. 1.10.6 (a) Before fractionated CO₂ resurfacing. (b) After fractionated CO₂ resurfacing
multiple available chromophores, including hemoglobin, deoxyhemoglobin, melanin and water. Lasers and light sources emitting wavelengths between 755 and 1,064 nm are commonly used for hair removal. With increasingly longer infrared wavelengths, water becomes the predominant target.

Lasers and light source utilizing these wavelengths are largely attempting to remodel collagen by heating dermal water and causing some initial denaturation and eventual repair of the collagen. Although a direct heat effect on collagen has been noted, there are other mechanisms at play such as the role of inflammatory cytokines stimulating human skin fibroblasts to upregulate the production of extracellular matrix proteins and matrix metalloproteinases.

1.10.7 Currently Available Technologies

1.10.7.1 1,064 nm Nd:YAG Laser

One of the first attempts at nonablative resurfacing utilized the Q-switched 1,064 nm Nd:YAG laser for periorbital or perioral rhytides. At high fluences (5.5 J/cm²), some patients appeared to improve almost as much as ablative laser resurfacing. However the treatment was complicated by pinpoint bleeding, petechia, and occasional purpura. Lower fluences led to fewer postlaser concerns, but also less improvement. The 1,064 nm Q-switched Nd:YAG laser has also been used in the treatment of atrophic acne scarring with some success.

Long pulsed Nd:YAG lasers, in the millisecond domain, are free of the petechial and purpuric effects seen with frequency doubled Q-switched Nd:YAG lasers. Such lasers have been used for deeper vascular lesions as well as rejuvenation. In general, many treatments are required and changes are often subtle.

A group of lasers, emitting wavelengths between 1,300 and 1,600 nm, have been used to nonselectively target the dermis, by using water as the target.

1.10.7.2 1,320 nm Nd:YAG Laser

This laser was the first of the infrared water targeting lasers used for facial rejuvenation [86–96]. This 1,320 nm wavelength has a high scattering coefficient and produces a general rise in dermal temperature inducing a wound healing response that leads to collagen denaturation and disruptions in collagen linkage. New collagen formation and collagen remodeling are seen by both histologic and clinical analysis [33–35]. Although there was early concern about short-term limited efficacy seen with this laser, longer lasting results have now been documented.

A number of studies have also shown a statistically significant, but relatively limited, subjective and objective improvement in atrophic acne scarring after three to six treatments performed at monthly intervals [36]. However other studies have noted less impressive results.

1.10.7.3 1,450 nm Diode Laser

The 1,450-nm diode infrared laser has been utilized in the treatment of acne, sebaceous hyperplasia, early rhi-nophyma, and periorbital rhytides [37].

The use of this laser for the purposes of photorejuvenation has been documented in women with periorbital and perioral rhytides who were treated four times at monthly intervals. Clinical and histologic analyses were undertaken both from treated and untreated control facial sites before treatment, immediately after the first treatment, and 3, 6, and 12 months after the fourth treatment. An increase in collagen synthesis and deposition was noted up until 6 months after treatment. No further increase in collagen formation was evident at 12 months after the last treatment. Although there was a significant degree of hypopigmentation noted in the study, the investigators felt that this was due to the laser-associated cryogen delivery, rather than from the laser itself.

The 1,450 nm diode laser effect on wrinkles has also been confirmed in other studies. In one of these studies, clinical improvement occurred in 13 of 20 patients, 6 months after two to four treatments when the laser was used in conjunction with cryogen; no improvement occurred when cryogen cooling alone was used.

A significant number of studies have also evaluated the effect of this laser on acne induced scarring. In a study comparing the 1,320 nm and 1,450 nm lasers for the treatment of atrophic acne scarring, a significant
improvement was seen after treatment with both lasers; 1,450 nm laser appeared to produce superior results.

1.10.7.4 1,540 nm Erbium: Glass Laser

The Erbium:glass laser emits a wavelength of 1,540 nm. Like the other mid-infrared lasers described above, this laser targets dermal water through an optical fiber. One study was conducted over five treatments at 6-week intervals of perioral and periorbital rhytids. The 42 female study subjects showed improvement 6 months into the study and exhibited significant increase in dermal thickness. In another study on perioral and periorbital rhytides in 24 women, a gradual, mild to moderate improvement was noted. Six months after treatment, increased dermal thickness was evident on histology. A study treating necklines and forehead rhytides of 20 female patients reported improvement in both skin tone and texture. Ultrasound evaluation showed that the neck and forehead had increased dermal thickness.

1.10.7.5 Fractional Photothermolysis

A laser concept termed “fractional photothermolysis” has also been developed to describe small vertical zones of full thickness thermal damage that are produced by a mid-infrared laser. This laser effect is akin to sinking posts or drilling holes of thermal damage with areas surrounding these posts left free of damage. This is not really a true nonablative method, but is a means of ablative resurfacing without the patient having to experience the pronounced healing phase seen after either truly ablative CO₂ or erbium laser resurfacing. This fractionated laser approach appears to show promise in the treatment of both epidermal and dermal disease processes. In addition, and in contrast to the effect of mid-infrared lasers, fractionated resurfacing also leads to improvement in epidermal dyschromias. The major indications for fractionated treatment include melasma, acne scarring, rhytids, and other signs of photodamage. This laser approach may also have some advantage over other approaches for the treatment of melasma, as well as its ability to be used on nonfacial areas to treat both epidermal and dermal photoaging. In such areas ablative resurfacing would be ill-advised. Surgical scars have also recently been successfully treated with this approach.

There are now a number of technologies that can be used for fractionated resurfacing. The most well-know laser uses a 1,550-nm wavelength. Other fractionated laser approaches involve the use of wavelengths of either 1,550, 2,940, or 10,600 nm (Fig. 1.10.6b).

Several different lasers and light sources have been used for PDT. Human tissue has the highest absorption for ALA in a spectral range of 600–800 nm. However, numerous other wavelengths can, and have been, successfully used.

There are, at this time, no established guidelines for a standard optimal irradiance, wavelength, and total dose characteristics for PDT. Commercially available light sources, utilized for PDT, have appropriate red or blue light emission designed for treatment of large areas. Most studies, which have employed ALA for PDT, have used red light. Red light is capable of deep skin penetration and can activate porphyrins produced by ALA and MAL.

Blue light is commonly used for the successful treatment of nonhyperkeratotic actinic keratoses of the face and scalp. Some reports have also demonstrated a good response with its use for the treatment of superficial and nodular basal cell carcinoma.

Lasers have also been employed in PDT for the curative treatment of actinic keratoses, superficial basal cell carcinoma, Bowen’s disease, and even as palliative treatment for cutaneous metastases in some patients.

1.10.8 Complications to Avoid

Complications can occur with any laser, light source or PDT approach.

In general, one wishes to avoid infections, scarring, and pigmentary disorders. Pigmentary changes can take the form of hypo or hyperpigmentation. Hyperpigmentation is more common in olive skinned patients and is usually temporary. Hypopigmentation can be temporary, but may also be permanent. A solid understanding of laser physics will lead to a markedly decreased incidence of treatment induced complications.
1.10 Laser Therapy

1.10.9 Global Variations

Despite the many varied currently available lasers and lights sources in all four corners of the world, basic approaches to treatment are fairly uniform. Thus PDT treatments or laser approaches to skin conditions do not markedly vary from one part of the world to another. The major variations relate to a greater incidence of complications in darker complected individuals and the development of today’s highly successful laser approaches to treat ethnic skin.

References


Take Home Message

➢ The future of laser and light technologies is clearly one of continuing expansion of both indications and new technologies. There is likely to be continued erosion of indications for ablative treatment with a gradual shift to nonablative therapies. Such a transition will also involve fewer required treatments and with a continuing improvement in safety profile. In addition, one can expect a continued growth of alternatives to lights and lasers as seen with radiofrequency and plasma treatments. Innovative “intelligent” handpieces should be expected. Better anesthetic creams and better cooling devices may also lead to easier patient treatments. Fractional photothermolysis involving multiple wavelengths is likely.

➢ Larger delivery heads, more powerful machines allowing more rapid treatment, and various combinations of lights and radiofrequency may occur. Multiplatform machines either offering many lasers within one unit, or containing lasers and lights within individual detachable handpieces, will continue to expand. One should also expect further refinement of PDT. Finally, additional skin chromophores, such as those in fat, may be found and more specifically targeted either singly or in combination with plasma, ultrasound, radiofrequency and new light-based treatments.

➢ Lasers, laser-like technologies and PDT approaches continue to grow as primary therapeutic modalities for many skin conditions, offering advantages of excellent cosmetic outcome and outstanding results. New indications will continue to emerge as research and clinical trials continue to offer new techniques and concepts to improve the efficacy of these treatment options.
device for reversal of photoaging: digital microscopic and clinical results in various skin types. J Drugs Dermatol 3: 605–610
1.11 Photodynamic Therapy

Yoshiki Tokura and Shin-ichi Moriwaki

1.11.1 History and General Concept

Photodynamic Therapy (PDT) involves administration of a tumor-localizing photosensitizing agent and following photoactivation of the agent by light of a specific wavelength. This treatment exerts a therapeutic effect on tumor tissues as a result of photochemical reactions. More than 25 years ago, PDT was proposed as a useful tool in oncology. Since 1993, regulatory approval for PDT has been obtained by using commercially available hematoporphyrin derivative compound (Photophrin®) in Canada, Netherlands, France, Germany, Japan, and USA for the treatment of cancers of respiratory, digestive, and genitourinary tracts. Many countries have been following these countries. In parallel, knowledge of the mechanisms underlying PDT has advanced, and efficient, convenient, and inexpensive systems of light delivery are now available [1, 2].

Terminologically, it appears to be difficult to ultimately distinguish PDT from photochemotherapy, and PDT may be included in photochemotherapy. However, PDT is based on the photooxidative action of photosensitizing agents, and its term is used for phototherapies with porphyrin derivatives. On the other hand, photochemotherapy is caused typically by photoconjugation of DNA or other cellular elements with the agents, and PUVA therapy or extracorporeal psoralen photochemotherapy belongs to this nomenclature.

PDT has several potential advantages over surgery and radiotherapy. It is comparatively noninvasive and targets the lesion accurately. Moreover, repeated doses can be given without the total-dose limitations associated with radiotherapy, and the healing process results in little or no scarring. Thus, PDT has been getting popularity in several clinical fields, although patients need to avoid sun exposure because of the transient generalized photosensitivity caused by the systemically administered agent. More recently, topical skin application of 5-aminolevulinic acid (5-ALA) and light irradiation has been used for skin malignancies. Since systemic photosensitivity, a major side effect of systemic PDT, is absent, topical PDT is relatively easy.

---

Key Features

- Photodynamic therapy (PDT) is one of the light-based therapies and is generally accepted in many countries.
- The treatment consists of administration of photosensitizers and following irradiation with light.
- There are both systemic and topical PDTs. While porfimer sodium and temoporfin are the photosensitizers for systemic PDT, 5-aminolevulinic acid or its derivatives are employed for topical PDT.
- Topical PDT has been developed in dermatology to treat nonmelanoma skin cancers or premalignant lesions.
- A photosensitizer, light, and resultant reactive oxygen species induce cellular damage, mainly apoptosis, and its therapeutic efficacy is enhanced by the destruction of vasculature and the immunological response to tumor antigens.

Y. Tokura (✉)
Department of Dermatology, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yhatanishi-ku, Kitakyushu 807-8555, Japan
E-mail: tokura@med.uoeh-u.ac.jp
and now expanding in its applications to even inflammatory skin diseases [3,4].

1.11.2 Systemic PDT

1.11.2.1 History and Current Status

Historically, systemic PDT with porphyrin derivatives as photosensitizing drugs was developed in early 1960s [2,5], when Lipson and Schwartz observed that injection of crude preparations of hematoporphyrin led to fluorescence of neoplastic lesions visualized during surgery. Schwartz treated hematoporphyrin with acetic acid and sulfuric acid and obtained porphyrin mixture, which was termed hematoporphyrin derivative. For the therapeutic use, this derivative was partially purified to form porfimer sodium [6]. This triggers the use of PDT in brain tumors, ophthalmological diseases, urological tumors, pancreatic and biliary tract carcinomas, esophageal premalignant lesions (Barrett’s esophagus), internal hemangiomas, and nonsmall cell lung carcinoma. Two photosensitising drugs, porfimer sodium (Photofrin®) and temoporfin, have now been approved for systemic administration, and they exert good therapeutic effects [2].

1.11.2.2 Complications to Avoid

A major disadvantage of Photofrin-mediated systemic PDT is photosensitivity for several weeks after cessation of the treatment. This is important for dermatologists, because we may have to suggest the duration of sun protection. The duration of photosensitivity was analyzed in relation to the patient’s sex, skin phototype, site of tumor, and liver function [7]. There was no correlation of the photosensitivity persistency with the site of cancers and the function of liver. However, female subjects needed significantly longer recovery periods than male subjects from potential photosensitivity after PDT. Patients with skin phototype 2 were significantly more sensitive than those with skin phototypes 3 and 4. Thus, a prolonged photosensitivity occurs after PDT, especially in female patients and in cases with a lighter skin type.

1.11.3 Topical PDT

1.11.3.1 History and Current Status

The easy access of skin to light-based therapy has led dermatologists to apply PDT to cutaneous disorders. 5-ALA-mediated PDT is probably one of the most selective cancer treatments currently known in skin oncology [4,8–22]. The introduction of 5-ALA does not induce strong generalized cutaneous photosensitization like the systemically applied porphyrins or their derivatives, and thus has reduced morbidity associated with PDT. The topical administration of 20% 5-ALA is usually employed especially for the treatment of nonmelanoma skin cancers [2,4].

Currently, two derivatives of 5-ALA, methylaminolevulinate (MAL) and hexylaminolevulinate (HAL) gained marketing authorization from the regulatory offices in Europe and Australia [11]. MAL is marketed under the trade name Metvix®, which is licensed in Europe for basal cell carcinoma (BCC) and thin or nonhyperkeratotic and nonpigmented actinic keratoses (AK) on the face and scalp, where other therapies are unsuitable [23]. HAL has recently been launched under the trade name Hexvix® for the improved diagnosis of superficial bladder cancer in Europe. Using a portable PDT light source, a more convenient service became available for patients [21].

1.11.3.2 Application to Nonmelanoma Skin Cancers

In dermatology, topical PDT has been most successful in treating AK, BCC, and Bowen’s disease [1,8–18,21,22,24]. Since these diseases characteristically affect older patients who may also have associated difficulties with mobility, PDT is an excellent choice in these patients. In our early study, 20% ALA was topically applied under occlusion to the sites of AK or Bowen’s disease for 3 h. The lesions were then irradiated with an Excimer laser. Each patient was treated
weekly 2–3 times. Good therapeutic effects were found in ?% of AK and ?% of Bowen’s disease (Fig.1.11.1).

Cure rates reported for very superficial lesions (tumor thickness <2–3 mm) are comparable to those achieved by other therapeutic modalities [21]. In superficial BCC and Bowen’s disease, several studies have reported complete response rates of 80–95% and an excellent cosmetic outcome [10]. An open, uncontrolled, prospective, multicenter study, in which patients with superficial and/or nodular BCC received one or two cycles within 3 months of topical MAL-PDT, each consisting of two treatments 1 week apart, showed that the lesion remission rate at 3 months was 92% for superficial BCC, 87% for nodular BCC, and 57% for mixed BCC, as assessed by clinical examination, and 85, 75, and 43%, respectively, as assessed by histological examination [15]. Patients with nevoid BCC syndrome were also well controlled with PDT [16]. In extension of Bowen’s disease, squamous cell carcinoma in situ is also well treated with PDT with excellent cosmesis, compared to 5-fluorouracil ointment and cryotherapy [18].

1.11.3.3 Approaches to Inflammatory Skin Disorders and Photorejuvenation

There are promising medical fields for the use of 5-ALA derivatives, potentially beneficial for the further progress of this methodology in photomedicine. Besides neoplastic skin diseases, PDT has recently been used for inflammatory skin disorders, such as psoriasis [13], cutaneous T-cell lymphoma [13], acne vulgaris [3,20], warts, morphea or scleroderma [8], and granuloma annulare [8], and sarcoidosis [14]. There have been considerable reports on these usages.

In acne vulgaris, 20% ALA cream was applied under occlusion to the sites for 3 h. Red light from a diode laser was then delivered to PDT [20]. Each patient was treated weekly for 3 weeks. There was a statistically significant reduction in inflammatory acne lesion counts from baseline after the second treatment. No statistically significant reduction in *P. acnes* number or sebum excretion was demonstrated. Even nodular and cystic acne show excellent therapeutic outcomes [9].
In psoriasis, one plaque was selected in each patient and treated once weekly with PDT two to five times [12]. PDT improved psoriasis and induced dermal neovascularization. Although a good clinical response was seen in most of those patients, the high frequency of discomfort during treatment limits the usefulness of 5-ALA-PDT for psoriasis.

The use of 5-ALA-PDT with short-contact, full-face broad-application therapy is a cosmetic dermatologic surgery or photorejuvenation [3, 4, 14, 17, 24].

### 1.11.3.4 New Modalities

Targeted PDT offers the opportunity of enhancing photodynamic efficiency by directly targeting diseased cells and tissues. While antibody-conjugates have received the most attention, cellular transformations offer numerous other potent targets to exploit during the delivery of photosensitizers for PDT. Alterations in receptor expression, increased levels of specific cell surface membrane lipids and proteins as well as changes in the cellular microenvironment all occur in diseased cells. Along with other biochemical and physiological changes that occur during diseased and malignant cell transformation, these factors have been utilized in order to improve the efficacy of PDT [25].

With the aim of improving the tumoritropic behavior of photosensitizers, liposomes are presently being used as carrier and delivery systems for PDT [26]. In general, conventional liposomes carrying photosensitizers are not able to establish elevated tumor-to-normal tissue ratios, hampering their generalized use as tumoritropic carriers of photosensitizers. Conversely, liposomes with a specifically modified design, i.e., long-circulating and especially, actively targeting liposomes, stand a better chance in becoming truly tumoritropic carriers of photosensitizers.

### 1.11.3.5 Complications to Avoid

Although topical delivery of ALA avoids the prolonged photosensitivity reactions associated with systemic administration of photosensitizers, its clinical utility is influenced by the tissue penetration of applied drug and the stability of the active agent [27]. Therefore, the effectiveness is strongly dependent on the surface conditions of lesional skin. The most common side effect of PDT is pain, burning or stinging discomfort at the site of treatment, although most patients do not request pain relief.

### 1.11.3.6 Photodynamic Diagnosis with Topical Application of ALA

In addition to PDT, ALA is used for estimation of the extent of malignant lesions [28]. Since ALA is selectively incorporated by tumor cells, one can see the boundaries between tumor and normal tissues. Observation of surface fluorescence 3 h after photosensitizer application can be utilized for tumor detection as well as delineation. This is especially beneficial for AK, whose lesional margin is often difficult to make clear. Although PDT is not a suitable therapeutic choice for extramammary Paget’s disease, it is useful for mapping of lesional area.

### 1.11.4 Mechanisms of PDT

#### 1.11.4.1 Photodynamic Action: Induction of Apoptosis of Tumor Cells

The cytotoxicity induced by a photosensitizer, light, and molecular oxygen is the major mechanism of PDT [5]. When localized in the target tissue, the photosensitizer is activated by light to produce reactive oxygen intermediates that destroy target cells. In topical PDT, ALA acts as a prodrug and is absorbed and converted by the hem biosynthetic pathway to photoactive protoporphyrin IX, which accumulates preferentially in rapidly dividing cells. Reactive oxygen species produced during this process cause cellular damage and, depending on the treatment dose/severity of damage, lead to either cellular repair/survival, apoptotic cell death or necrosis [27, 29–31]. The caspase-3 activation starts immediately after the PDT treatment [32]. Activation of caspase 9 and cleavage of poly (ADP-ribose) polymerase (PARP) induce subsequent DNA fragmentation [33]. The level of endoplasmic reticulum Ca-binding
1.11 Photodynamic Therapy

1.11.1 Photodynamic Therapy

Chaperones ERp57 and ERp72 and of anti-apoptotic proteins Bcl-2 and Bcl-XL is decreased, whereas that of Ca-binding protein calmodulin and the stress protein HSP60 is elevated following ALA-PDT [33]. Mitochondria are central coordinators of the mechanisms by which PDT induces apoptosis in the target cells [31, 34–36] (Fig. 1.11.2).

1.11.4.2 Effects on Tumor Stroma

A tumor consists of two fundamental elements, neoplastic cells and stroma. The stroma is composed of vasculature, cellular components, and intercellular matrix and is necessary for tumor growth. All the stromal components can be targeted by PDT [37]. Although the exact mechanism of PDT is unknown, emerging evidence has indicated that effective PDT of tumor requires destruction of stroma as well as neoplastic cells. Furthermore, damage to subendothelial zone of vasculature, in addition to endothelium, also appears to be a crucial factor.

1.11.4.3 Induction of Inflammation and Antitumor Immunity

PDT initiates an inflammatory response that will indirectly contribute to tumor clearance. The status of NF-kappaB transcription factor is altered following photosensitization in cancer cells and endothelial cells [38]. NF-kappaB is a major regulator of inflammation modulating the expression of cytokines, chemokines and adhesion molecules in various cell types in response to a large number of stimuli. It also regulates the expression of anti-apoptotic genes, cyclooxygenases and metalloproteinases as well, thereby favoring tumor cells proliferation and dissemination.

PDT causes or enhances an antitumor response. PDT of cancer is a way of in situ vaccination to induce a systemic antitumor response. It has been hypothesized that PDT destroys the structure of a tumor, thereby enabling direct interaction between immune cells and tumor cells resulting in the systemic antitumor immune response [39].

1.11.4.4 Susceptibility of Cells to PDT

Immortalized cell line cells that express only mutant p53 were found to be more resistant to PDT compared to normal human fibroblasts [40]. This suggests a role for p53 in the response of human cells to PDT. On the other hand, in Photofrin-mediated PDT, the level of expression of low-density lipoprotein receptors influences the sensitivity to killing in cultured human tumor cell lines [41, 42].

Take Home Message

› Topical PDT using 5-ALA or its derivatives are an important therapeutic choice for the treatment of AK, BCC, and Bowen’s disease especially in older patients.

1.11.5 Global Variations and Operative Procedure

As photosensitizers for topical PDT, MAL and HAL gained marketing authorization from the regulatory offices in Europe and Australia [11], and 20% 5-ALA is also used in other countries. These photosensitizing products are applied to skin lesions, and closed
dressing is kept for 4–7 h. Then, the lesions are irradiated with visible light containing 630 nm. During irradiation, patients may have burning and/or pain, but it is tolerable without anesthesia. Immediately after irradiation, the irradiated skin is erythematous and edematous, and gradually becomes crusty (Fig. 1.11.1). One to 2 weeks later, crusted lesions are healed. As light source, excimer dye laser is frequently used in Japan. Red light from a diode laser and YAG-OPO laser are other choices. Recently, portable PDT light source is employed. In USA, halogen lamp (BLU-U Blue Light Therapy Illuminator) is popular. The irradiation dose at each time is 100–200 J/cm². When this is not effective, the operation can be repeated several times.

References

Sentinel lymph node biopsy is becoming a standard of care prognostic procedure for melanoma of depth greater than 1 mm.

Bilayered repairs reduce the risk of dehiscence and provide improved cosmesis postoperatively.

Local anesthesia, commonly lidocaine with epinephrine, is sufficient for most dermatologic procedures.

Topical anesthetics and nerve blocks may be appropriate adjuvant anesthetics in special situations.

Surgery in children, such as removal of congenital nevi, may require general anesthesia.

1.12.1 Etiology and Pathogenesis

The etiology of skin cancer, including nonmelanoma and melanoma skin cancers, is discussed elsewhere. For patient education, it is important to communicate that pre-existing fair skin and genetic predisposition are not reversible, but continuing sun exposure is susceptible to behavioral change. Additionally, patients should understand that while basal cell carcinomas and squamous cell carcinomas seldom cause loss of life, the growth in size of these untreated tumors can be slow but inexorable, with delayed presentation potentially greatly increasing the risk of disfigurement and functional loss [2, 17, 19]. Patients are also frequently curious about the cause of benign lesions, such as cysts and lipomas. It may be helpful to communicate that these can be familial, but are almost inevitably harmless. Such reassurance can help dimin-
ish the anxiety of a patient who serially develops several benign growths.

1.12.2 Clinical Characteristics and Diagnosis

Skin biopsy of inflammatory or neoplastic lesions is preceded by diagnosis of these lesions as abnormal. Features consistent with such diagnosis include: rapidly growing course; dissimilarity from surrounding lesions (e.g., “ugly duckling” sign); history of prior skin cancer presenting similarly; large size; persistence of greater than 1 month at the same site; invasion or impingement of surrounding structures (e.g., hair loss, effacement of facial sensory structures, restriction of digital range of motion); pain or discomfort; bleeding or serous drainage.

Shave biopsy is appropriate when lesions are pedunculated or protuberant. Punch biopsy is appropriate for lesions that are sessile or have a significant deep component. Incisional biopsy may be appropriate for large lesions of indeterminate provenance: an incisional biopsy is similar to an elliptical excision that removes only a subtotal portion of the lesion, and is useful for providing a large amount of deep tissue for histologic examination [2, 3].

Excisional surgery is most appropriate for well-defined skin cancers as well as for certain benign lesions. Well-defined skin cancers include nonmelanoma skin cancers meeting the following criteria: on the head and neck, small size (5 mm or less), well-defined borders, and superficial growth pattern; on the trunk and extremities, size less than 2 cm, primary lesions, no involvement of genitalia, muscle, or hands/feet, and no concurrence of immunosuppression, aggressive histology, or ionizing radiation exposure history. Nonmelanoma skin cancers meeting these criteria may also be treated by cryosurgery or electrodesication and curettage. Nonmelanoma skin cancers not meeting these criteria may be treated by Mohs micrographic surgery, an advanced tissue-sparing technique that ensures microscopic margin control [17, 19]. Rare, aggressive nonmelanoma skin cancers may require special management. Specifically, merkel cell carcinoma management approximates that of thicker melanomas, with wide local excision followed by possible sentinel lymph node sampling, and possible local irradiation.

Benign lesions may also be treated with excision. Cysts, including pilar and epidermoid types, and lipomas are easily clinically diagnosed by palpation, visual assessment, and history. Biopsy is seldom necessary to establish diagnosis. Excision can therefore proceed immediately, with conservative margins to minimize tissue injury. Cysts and lipomas are often removed when they are inflamed, infected, sclerosed, recurrent, or ruptured (cysts); or if they are associated with difficulty in combing hair or loss of hair (pilar cysts); or if they are unsightly or induce pain upon activities of normal living (cysts and lipomas).

Atypical nevi and melanocytic lesions suspected of being melanoma are also excised in toto. Complete excision is necessary since nevi and melanoma are potentially nonhomogenous lesions. Partial removal could theoretically fail to harvest the most atypical focus, and hence lead to under-staging and inadequate treatment of the overall lesion. A conservative excision margin of 1–3 mm is appropriate for suspicious but not previously histologically assessed melanocytic lesions.

Previously diagnosed melanomas are removed by wide local excision. Depth is to muscular fascia, and the peripheral margins are contingent on the histologic assessment of the tumor. In situ lesions require a 0.5 cm peripheral margin, or may be excised by Mohs surgery. Shallow melanomas may be excised with a peripheral margin of 1 cm, and Breslow depth of greater than 1–2 mm may be removed with a peripheral margin of 1–3 cm. Sentinel lymph node biopsy is indicated in the US for melanoma deeper than 1 mm. Adjuvant chemotherapy regimens may be available to patients after surgical management is complete.

Local anesthesia is used for most dermatologic procedures. The most common variant is lidocaine 0.5–2.0% solution with 1:100,000–200,000 epinephrine. Injectable lidocaine solutions are typically used for skin biopsies, excisional surgery, and Mohs surgery. Very large Mohs procedures, excisions, and liposuction may be performed using so-called tumescent anesthesia. Tumescent anesthesia is an extremely dilute solution of lidocaine (0.1–0.05%) that provides anesthetic effect, hemostasis, and when necessary, hydrodissection of fat. Small superficial lesions such as cherry angiomata, seborrheic keratoses or skin tags can be electrodesiccated or shave excised with topical anesthesia alone. Topical anesthesia may also be used prior to soft-tissue augmentation injections or nonablative
laser, light, and radiofrequency, and ultrasound procedures that target the dermis and subcutis but secondarily heat the epidermis [1]. While topical anesthetic formulations vary, common ointments and creams include 1–10% concentrations of lidocaine, tetracaine, or other anesthetics. Topical anesthesia is not indicated for use on mucosal surfaces and should be used on limited body surface areas without prolonged occlusion since systemic absorption can occur.

By directly targeting a major sensory nerve trunk, nerve blocks create anesthetic effect over a large surface area with a single injection of a modest quantity of solution. Nerve blocks are used most often for extensive facial surgery, as well as for surgery on the hands and feet. Excisional or Mohs surgery on the face, as well as facial soft-tissue augmentation, may be made more comfortable with nerve blocks. Infraorbital blocks are indicated for surgery of the medial cheeks, and ipsilateral nasolabial folds and lips. Mental nerve blocks provide anesthesia to the ipsilateral lower lip and chin. On the hands and feet, nerve blocks may be initiated prior to surgical excisional, injection of botulinum toxin for hyperhidrosis, or soft-tissue augmentation.

Melanoma is rare in children, but melanocytic lesions are ubiquitous. To forestall the future malignant degeneration of large congenital nevi into melanoma, or nevus sebaceous into syringocystadenoma papilliferum or basal cell carcinoma, excision may be undertaken in childhood. Lesions are smaller in children, and scars heal better at this age. Usually, excision is under general anesthesia or conscious sedation. In the US, specialized pediatric dermatologic surgeons may perform such surgeries. Laser procedures for treatment of hemangiomas and vascular lesions in children may also be performed under general anesthesia.

### 1.12.3 General Therapeutic Outline

Skin biopsy is performed for inflammatory and neoplastic lesions not definitively diagnosed by clinical assessment.

Surgical excision is the workhorse of dermatologic surgery. Excision is appropriate for benign lesions that are associated with symptoms or functional impediment (e.g., cysts, lipomas), less aggressive nonmelanoma skin cancers off the head and neck, and worrisome melanocytic lesions. Low risk nonmelanoma skin cancers may also be destroyed by other methods, most notably electrodessication and curettage.

Mohs surgery is performed for nonmelanoma skin cancers of the head and neck, high risk nonmelanoma skin cancers of the trunk and extremities, and lentigo maligna (melanoma in situ) [10, 12-16, 20-22]. Mohs is more tissue-sparing and provides more precise histologic margin control than standard excisional surgery. The greater cost and resource utilization of Mohs restricts its use to malignant tumors of specific types [6].

Suspected melanomas should be excised to subcutis with conservative margins. Previously diagnosed melanomas should be re-excised per protocol with wide local excision. Depth of excision is to fascia, and width is 0.5–3 cm, depending primarily on Breslow depth. Sentinel lymph node biopsy may be appropriate for histologically diagnosed melanoma greater than 1 mm in depth.

Local anesthesia is an exceedingly safe and effective modality that enables most dermatologic surgeries. Usually subcutaneous or intradermal injections of a few mLs of lidocaine with epinephrine are sufficient to induce anesthesia and provide hemostatic benefits. Larger surgeries in selected areas may be simplified by use of nerve blocks or tumescent anesthesia. Topical anesthesia has limited applications in excisional surgery but may be used before soft-tissue augmentation and laser procedures.

Congenital nevi and precancerous lesions in children may be excised by specialized dermatologic surgeons under general anesthesia. Vascular laser and lights may also be used to treat hemangiomas and other vascular lesions in this patient population.

### 1.12.4 Current Established Therapies

#### 1.12.4.1 Skin Biopsy

The most common types of skin biopsy are shave and punch biopsies, respectively. In shave biopsy, a #15 blade or similar device is used to cut a lesion tangential to the skin margin. Pedunculated or protuberant lesions are sampled in this manner. Insufflation of
dermis with local anesthesia can also cause a raised dimpling of the skin which permits shave biopsy in essentially flat lesions. Following acquisition of the shave specimen, hemostasis is achieved with aluminum chloride solution, Monsel’s solution, light electrocautery, or pressure dressing.

Punch biopsy is most appropriate for flat lesions and for sampling deep dermis or subcutis. A round coring device with sharp edges is used to remove a cylindrical piece of epidermis, dermis, and subcutis. The resulting hole is usually sutured shut with one or more simple interrupted sutures. Larger diameter punches (5–8 mm), may require the placement of a deep absorbable suture as well.

Excisional biopsy can be performed for cosmesis or preservation of function in sensitive areas. In this procedure, a very thin wedge of tissue is removed and then closed with one or several simple interrupted sutures. Unlike a shave biopsy, an excisional biopsy avoids creating a depression and successfully samples deep dermis; unlike a punch, an excisional biopsy avoids creating dog-ears because it conforms to a 3:1 length to width ratio typical of surgical ellipses.

Incisional biopsies are performed to sample a deep and possibly wide portion of a much larger lesion. Incisional biopsies are often obtained when a significant quantity of tissue or deep subcutis is required for diagnosis. Such biopsies may be the size and shape of a standard elliptical excision but cannot be called an excision because they do not remove the whole lesion.

### 1.12.4.2 Elliptical Excision

An elliptical excision is the standard surgical removal method used in dermatologic surgery [5]. An oval piece of skin including epidermis, dermis, and at least partial thickness subcutis is removed using a #15 or #10 blade. The resulting defect is closed with suture repair. Elliptical excisions that are larger than 1 cm are usually closed with a bilayered repair, including absorbable dermal sutures to close the deep dermis and fat, and absorbable or nonabsorbable epidermal sutures to close the epidermis. Nonabsorbable epidermal sutures are removed in 5–10 days on the face, and 10–21 days elsewhere on the body.

Much has been written on the design of the optimal elliptical excision. Among the most crucial features is the length to width ratio. A ratio of 3:1 or 4:1 is associated with minimal dog-ears, or residual puckers at the edges of the excision. However, careful technique permits expert surgeons to use a ratio as low as 2.5:1, allowing a shorter overall scar length. Undermining, or separating the dermis from the subcutis by scissors or sharp dissection in the horizontal plane so that the former slides unobstructed and untethered into place, can improve the appearance of an elliptical closure. Undermining reduces the likelihood of persistent visible dog-ears several weeks after the procedure. Wide undermining 1–3 cm around the entire ellipse is most effective. Bleeding is often initiated by vessel trauma secondary to undermining; cautery, pressure, and suture ligation of vessels may be necessary to control this. An elliptical excision should not be sutured shut until any rapid bleeders, so-called “pumpers,” have been stopped.

Suturing of an elliptical excision is to achieve a thin, flat final scar. To this end, the wound closure should be everted. That is, the absorbable sutures are placed in such a manner that the wound edge protrudes like a gently undulating ridge. By minimizing tension on the wound edge, eversion prevents a stretched or pulled appearance of the final scar line. Since wounds heal by contraction away from the wound edge, the eversion will eventually recede, leaving a flat scar.

On the trunk and extremities, the top level repair of a bilayered elliptical excision may be by subcuticular suture. Subcuticular sutures are placed just under the epidermis, and run side-to-side without perforating the epidermis. As such, subcuticullars prevent the dot-like arrays or “track marks” that may be associated with prolonged placement of epidermal sutures. On the head and neck, wound healing is faster; as a consequence, subcuticular closures are less necessary for facial closures since even routine epidermal sutures are removed before track marks can appear.

Facial epidermal closures can be with simple interrupted sutures or with running sutures. The former are individually knotted and the latter are knotted only at the beginning and end of the run. Simple interrupted sutures may be preferred when more eversion is desired or when there are hemostatic concerns.

To strengthen elliptical excisions, adhesive tape dressings and tissue glues can be applied to the sutured wound. Pressure dressings may be used for 12–48 h to decrease the risk of immediate postoperative bleeding or hematoma formation. For the same reasons, and to
avoid dehiscence, patients may be asked to limit aerobic and anaerobic activities. Oral antibiotics are seldom indicated for prophylaxis, but oral pain medications may be considered for larger excisions.

1.12.4.3 Mohs Surgery

Mohs surgery is a tissue sparing excisional technique that histologically assesses 100% of the peripheral and deep margin. This is a staged process with intraoperative pathology using frozen section analysis. Most commonly employed for basal cell carcinoma [12, 14] and cutaneous squamous cell carcinoma [15, 16], Mohs can also be used for other rare nonmelanoma skin cancers [10, 13], melanoma in situ, and occasionally for invasive melanoma [22]. Nonmelanoma skin cancers treated by Mohs tend to be high-risk lesions or lesions at cosmetically and functionally sensitive sites on the head and neck, hands and feet, and genitalia.

Mohs begins when the clinically apparent tumor is marked, anesthetized, and surgically excised with a 1–3 mm margin. A temporary wound dressing is applied while the tissue is mapped, sectioned, frozen, cut, stained, mounted, and examined microscopically. Specimen preparation in Mohs differs from that in routine dermatopathology in that the tissue is not quartered or “breadloafed,” but rather is “skinned” so that the entire outer margin can be viewed. The surgeon is also the pathologist in Mohs. After the first “stage” of a Mohs procedure has been checked for margin positivity, an additional stage is taken by removing tissue at the points of positivity, or if the initial stage was clear at the margins, the defect is repaired. If another stage is taken, this is processed similarly to the first. Mohs continues until the wound is clear of tumor along all peripheral and deep margins.

1.12.4.4 Reconstructive Surgery [7, 8, 11, 18, 23]

Closure of final wound defects after Mohs surgery is commonly by second intent, primary repair, local flap, or skin graft. Second intent occurs when the wound is allowed to heal by itself, through the process of granulation. Areas that are curved inward, like the medial canthus and the conchal bowl of the ear, heal well by second intent. Shallow wide defects, such as those of the scalp, may also heal well in this manner. Primary repair is typically a bilayered closure, with layers of absorbable dermal sutures below a layer of epidermal nonabsorbable sutures. A primary repair may not be feasible if the defect is: very large; adjacent to a so-called free margin, like the lip or eyelid, which would be unacceptably pulled; at a site of minimal tissue laxity; or, such that there is a high risk of asymmetry or loss of sensory function. When a primary repair is suboptimal, a flap or skin graft may be most appropriate. A local flap is used when there is a nearby reservoir of lax tissue that can be moved into the defect. Each flap is an innervated area of tissue that remains connected to blood supply, known as the vascular pedicle. Movement of a flap into the defect is by advancement (i.e., sliding into place), rotation along an arc, or transposition. Interestingly, primary repairs can be alternatively described as advancement flaps with very broad vascular pedicles. Transposition entails movement of tissue over another area of tissue and into the wound defect; if reduced to a series of simple motions, transposition flaps usually include rotation or advancement. In dermatologic surgery, most flaps are random flaps, and as such based on no specific vessel. One notable exception is the paramedian forehead flap, which is a transposition flap harvested from the forehead, based on a unilateral supratrochlear artery, and for repair of full-thickness nasal tip defects. A special case of the advancement flap is the subcutaneous island pedicle flap, which is a triangular flap that is incised on all lateral margins and receives its vascular supply from a subcutaneous pedicle under the center of the flap. Meticulous hemostasis is necessary when constructing flap repairs.

At times, even a local flap is insufficient to repair a large defect. Broad, shallow defects that cannot be allowed to heal by second intent may be amenable to closure by skin graft. Skin grafts can be partial thickness, including epidermis but only part of the dermis, or full thickness, including the entire dermis. Partial thickness grafts can be larger and applied over areas with minimal vascular supply, but they tend to be cosmetically inferior, with a shiny, scar-like appearance. Most grafts used in dermatologic surgery are full-thickness grafts. Harvested from concealed, lax tissue reservoirs, like the post- or preauricular area, upper inner arm, or upper thigh, grafts are then transplanted
into the wound defect. The donor site may require secondary closure, or may be allowed to heal by second intent. Deeper defects on the nose may require so-called composite grafts, which include cartilage in addition to skin. Color and texture match of graft skin and the skin peripheral to the wound defect may be poor. Also, since grafts do not retain blood supply from the point of harvest, they are more fragile than local flaps, and can fail. Full-thickness skin grafts must be placed on defects with good vascular supply to increase the likelihood of graft survival.

1.12.4.5 Surgery in Children

Dermatologic surgery in children usually entails excision of congenital nevi. As such, the rules of elliptical excisions apply. Since postsurgical activity restriction is difficult to enforce in children, placement of a relatively greater number of dermal sutures may be necessary to reduce the risk of wound dehiscence.

1.12.5 Experimental Approaches

Dermatologic surgery for skin cancer is a relatively mature field. Advances are incremental, and focused on improving cure rates and minimizing scars.

In vivo imaging of skin cancers using confocal microscopy and other tools may eventually permit more precise cancer excision. Specifically, if the precise boundaries of a tumor could be noninvasively detected before an incision were made, only a single stage of Mohs would be required to extirpate the tumor.

Regarding reconstruction of cutaneous surgical defects, adult-derived autologous stem cells are being used to facilitate granulation of wide and deep defects. A soup of stem cells and mature skin cells, set in a chemical scaffold, may speed up healing at sites, like the lower leg, where spontaneous healing is slow and uncertain.

1.12.6 Complications to Avoid

Functional loss and disfiguration after cancer surgery of the face can be avoided by minimizing defect size and carefully selecting an appropriate reconstruction technique. Mohs surgery may be an appropriate tissue-sparing procedure for facial tumors, and also for other tumors in cosmetically and functionally sensitive areas. Reconstruction may require multiple stages to achieve optimal outcomes. Skin grafts may be delayed to allow partial granulation at recipient sites so as to avoid depressed final closures.

Prolonged application of topical anesthesia under occlusion over a substantial body surface area has been associated with methemoglobinemia and death. In the US, the American Society for Dermatologic Surgery has asked physicians to avoid the use of nonapproved topical anesthesia cocktails prepared by local pharmacies as some of these may be of uncertain strength.

In the treatment of melanoma, it is crucial to avoid leaving behind residual tumor. Following protocols for excision margin based on Breslow depth and other salient clinicopathologic features is highly advisable.

Take Home Message

Dermatologic surgical techniques permit safe and effective removal of skin cancers and problematic benign lesions with only local anesthesia. For high risk tumors near sensory organs, Mohs surgery can further preserve normal tissue while ensuring a high cure rate.

1.12.7 Global Variations

Use of Mohs surgery is more widespread in the US than in Europe, Asia, and Latin America. In some countries, major cutaneous reconstruction is seldom performed by dermatologists, and often referred to plastic surgeons.

Further Reading

Itch, generally defined as an unpleasant sensation eliciting desire or reflex to scratch [1], is a common symptom accompanying many cutaneous and systemic diseases and has been regarded to be a key therapeutic subject not only since unpleasantness lowers quality of life but also since itch-induced scratching worsens skin conditions or newly forms skin inflammation. However, there has been little progress in antipruritic therapies so far. Antihistamines have been widely applied as the first choice for any type of itch since decades, but mostly in vain except for some types like urticaria-associated itch. It is only in more recent times that itch has received research attention and our understanding of its mechanism has begun a rapid growth.

1.13.1 Neuronal Pathways for Itch: From Skin to Brain (Fig. 1.13.1)

Itch used to be generally believed to occur from weak activation of pain nerves. This so-called “intensity theory” had been broadly accepted until the nerves responding to histamine, the best-known pruritogen since half a century, were identified in primary afferent neurons of humans and spinal projection neurons of cats.

Primary afferents for histamine-induced itch belong to unmyelinated C-nerves but are different from the common type of C-nerves for pain that are mechano-sensitive (polymodal) [2]. They have a higher threshold for electrical stimulation and a larger innervating skin area than polymodal C-nerves. This supports the “specificity theory” that itch and pain are conducted in separate neuronal pathways. However, later studies show that they are reactive not only to histamine but also to capsaicin and some other pain mediators [3]. They are therefore termed as “itch-selective” nerves rather than “itch-specific” ones.

Histamine-sensitive neurons have also been recorded in cats and found in a small subgroup of spinothalamic projections [4]. Like histamine-sensitive primary afferents in humans, they do not respond to mechanical stimulation. Additionally, they do not have any spontaneous activity in contrast to other spinothalamic projection neurons involved in pain processing.
A. Ikoma

Mechano-insensitive nerves for histamine-induced itch cannot account for mechanically evoked itch that is clinically experienced. In addition, while histamine-induced itch is always accompanied by axon-reflex flare, itch without flare is commonly observed and can be experimentally generated by cowhage spicules [5]. This suggests the presence of other nerves for itch, which is also supported by a previous study reporting that itch can be evoked without flare formation by weak electrical stimulation of skin [6].

In succession to many brain-imaging studies related to pain sensations, some studies related to itch sensations have also been carried out. It has generally been accepted that spatial, temporal, and intensity aspects of pain perception are processed in the primary and secondary somatosensory cortex (S1 and S2, respectively), whereas its affective and motivational aspects in the anterior cingulate cortex (ACC) and the insular cortex [7]. The activation of thalamus, prefrontal cortex, premotor areas and cerebellum is also commonly observed with pain sensations [8–10]. As for itch sensation, it has been shown by studies using positron emission tomography (PET) that prefrontal cortex, premotor areas, S1 and ACC are activated in response to histamine-induced itch [11–13]. Predominantly ipsilateral activation of premotor areas is regarded to reflect the desire to scratch. A large overlap has been identified between pain- and itch-related brain areas. The main difference lies in the lack of S2 activation in itch sensations. However, since only several brain-imaging studies have been performed on itch-related activation, conclusive interpretation cannot be offered.

### 1.13.2 Interactions Between Itch and Pain

Inhibition of itch sensation by painful mechanical stimuli like scratching or pinching is a common experience. Painful electrical stimulation reduced itch for several hours at a distance up to 10 cm from the site where histamine was applied [14]. Itch was also suppressed inside the area with capsaicin-induced hyperalgesia [15]. These suggest a central mode of inhibiting action. Itch can be inhibited by noxious cold stimuli, but less than by noxious heat stimuli or scratching [16]. A paradoxical observation has also been reported that short-term moderate temperature decrease enhances itch in contrast [17].

On the other hand, analgesia reduces this inhibition and would enhance itch [18]. It is typically relevant to this that spinally applied morphine, an opioid μ-receptor agonist, is likely to inhibit segmental pain but induce segmental itch [19]. Opioid μ-receptor antagonists have been reported, on the contrary, to have antipruritic effects on cholestatic itch [20]. It is of note that the reduction of itch by naloxone, an opioid μ-receptor antagonist, is followed by induction of pain in some patients with cholestatic itch[21]. Meanwhile, antagonists to opioid κ-receptors enhanced itch in mice [22]. In addition, agonists to opioid κ-receptors have been found to reduce morphine-induced itch [23] and were effective in patients with uremic pruritus that is generally resistant to antihistamines [24]. It was shown that hemodialysis patients with severe pruritus have an increased ratio of β-endorphin/dynorphin A in their serum, which are respectively endogenous μ- and κ-receptor agonists [25]. This suggests that imbalance of endogenous opioids is related to pruritus of hemodialysis patients.
1.13.3 Peripheral and Central Neuronal Sensitization

Patients with chronic pain, for instance, postherpetic neuralgia often complain of pain evoked by weak mechanical stimuli like light contact of clothes to the skin. They also feel intense pain by light pin-pricking stimuli to the skin. These phenomena, called allodynia and pin-prick hyperalgesia respectively, are caused by neuronal sensitization, that is, lowering of neuronal thresholds. Corresponding phenomena are observed in patients with chronic pruritus. A typical example is that patients with atopic dermatitis (AD) often feel itch sensation, especially in their eczematous skin, by weak mechanical stimuli like contact of wool fibers to the skin. It was also shown that intracutaneous application of histamine induced significantly more intense itch in their eczematous skin than in their nonaffected skin and in healthy persons [26]. These phenomena, parallel to allodynia and hyperalgesia, are called alloknesis and hyperknesis, respectively, and are regarded to be also due to neuronal sensitization.

Peripheral inflammatory mediators like bradykinin, serotonin, prostaglandins and neurotrophins released in inflamed skin not only activate but also acutely sensitize peripheral neurons [27]. Sensitized peripheral neurons would react to those stimuli that normally induce no activation. Increased serum level of nerve growth factors (NGFs) has been reported to correlate with the severity of AD [28]. Sprouting of epidermal nerve fibers caused by increased neurotrophins, which might also contribute to sensitization, is found in patients not only with localized pain and hyperalgesia but also with AD [29,30]. This similarity suggests that similar mechanisms of peripheral neuronal sensitization exist both for painful and itchy lesions.

Ongoing activation of peripheral pain-C-nerves is known to lower thresholds of spinal processing neurons for pain in the spinal cord [31]. As a result, signals conducted through other peripheral nerves can also activate central neurons for pain. For example, signals conducted through A-β nerves, which normally evoke touch sensation, cause pain sensation. This accounts for allodynia. As for itch, itch evoked by transcutaneous electrical stimulation is accompanied by alloknesis [6]. This implicates that central neuronal sensitization is also involved in alloknesis. It can be assumed that ongoing activation of peripheral itch-C-nerves in patients with chronic pruritus, which has been reported [32], would cause central neuronal sensitization and lead to alloknesis.

The combination of peripheral and central neuronal sensitization causes not only slight nonitchy mechanical stimuli but also various painful stimuli, which normally inhibit itch, to induce itch. An experimental study has shown that itch can be evoked in patients with AD by mechanical, electrical, thermal and low-pH stimuli [33]. This finding is compatible with one of their well-known clinical features that they are often urged to continue scratching once they start it, suggesting that scratching does not inhibit but, on the contrary, generate itch. It is of note that neuronal sensitization for pain in patients with chronic pain results in a contrastive phenomenon that histamine exclusively induces pain instead of itch [34]. Thus, neuronal sensitization can give mediators roles different from their original ones.

1.13.4 Pruritogens

Histamine is the best-known pruritogen (= itch mediator) of humans. It was reported that histamine activates not only mechano-insensitive “itch” C-nerves but some polymodal “pain” C-nerves [3]. The pruritic potency of inflammatory mediators seems to be based both on activation of itch nerves and inactivation of pain nerves. Prostaglandin E2 (PGE2) is another substance that moderately activates itch C-nerves but hardly pain C-nerves. Actually, intradermal application of PGE2 in humans induced itch [35].

Tryptase is another mast cell mediator possibly acting as a pruritogen. Activation of protease-activated receptor-2 (PAR-2) by tryptase seems to be responsible for itch sensation, as PAR-2 is densely expressed at nerve endings of AD and its artificial ligand applied to AD was found to induce itch [36]. Activation of PAR-2 has been shown to take part in peripheral neuronal sensitization [37], which might also be related to the role of tryptase as a pruritogen.

Acetylcholine (ACh), when injected intradermally, induced pure itch sensations in patients with AD [38]. ACh is released from endings of sympathetic nerves innervating eccrine sweat glands and might therefore account for pruritus after sweating, of which some patients with AD complain. By the way, ACh normally
induces pain in human skin. Bradykinin is another inflammatory mediator that is generally known to be an algogen (= pain mediator) but induces itch intensely in patients with AD [39]. According to previous studies, neurotransmitters, proteinases and cytokines that do not induce itch in healthy persons also belong to candidate pruritogens of AD [40]. This difference between healthy skin and AD can be explained by neuronal sensitization in patients with AD. The potency of pruritogens is also intensified by neuronal sensitization, so that serotonin, a much weaker pruritogen than histamine, would induce a strong itch in the lesional skin of patients with AD [39]. It is interesting to note that histamine induces rather less itch in nonlesional skin of patients with AD than in healthy persons but much more intensely in their lesional skin [26].

Many animal experiments have investigated candidate pruritogens. For instance, leukotriene B4 has been shown to induce itch in mice [41]. However, if applying results of animal studies on itch to humans, racial differences should be taken into account. Histamine is a potent itch mediator in humans but not always in rodents [42]. On the other hand, although substance P is a histamine-independent potent pruritogen in rodents, human studies have rather denied its role as a pruritogen [43].

### 1.13.5 Pruritus of Origins Other Than Skin

Some types of pruritus cannot be explained by skin disorders and seem to have systemic origins such as metabolic disorders, hematological diseases, visceral tumors and drug application. Chronic renal failure and liver diseases with cholestasis are frequently accompanied by intractable pruritus [44]. The role of opioid peptides has been proposed in such pruritus, since μ-receptor antagonists and κ-receptor agonists had been reported to be effective [45,46]. However, the further mechanism remains to be investigated.

Postherpetic neuralgia causes not only pain but sometimes also itch [47]. This type of itch, called “neuropathic itch,” originates from neuronal disorders and includes pruritus associated with multiple sclerosis, notalgia paresthetica and brachioradial itch [48–50].

### 1.13.6 Therapeutic Targets

Histamine causes itch, flare and wheal locally when released in the skin from mast cells. Among histamine receptors, H1-receptors have been presumed to have a main role in these reactions. H1-receptor antagonists can suppress histamine-induced itch and are mostly effective for pruritus of some urticaria subtypes. However, they are little effective in many other pruritic diseases like AD [51]. Other histamine receptors such as H4-receptors might also be involved in histamine-induced itch, as was shown in mice [52], but their role in humans remains to be clarified.

The involvement of neuronal sensitization in pruritic diseases contains a therapeutic implication that not only pruritogens but also algogens should be targets to combat. From this point of view, the complete suppression of inflammation is rather shortcut than preparing antagonist drugs to overcome pruritus of skin origin like AD. Corticosteroids, tacrolimus and pimecrolimus are therefore the most effective for pruritus of AD.

It might also be worthwhile to focus on prevention of neuronal sensitization. Anti-NGF strategies have successfully been applied in both of mouse models [53] and patients with pain [54]. As for pruritus, anti-NGF approaches have been tried and found to be effective in NC/Nga mice, model mice of AD [55].

Pruritus of systemic origins is, generally speaking, intractable except by radical cure of original diseases, which is mostly difficult in reality. Since imbalance of endogenous opioids has been reported to play a major role in such itch [25], its correction draws attention as a therapeutic strategy. Agonists to opioid κ-receptors are expected to be of some help to pruritus of renal failure and other systemic origins.

Neuropathic itch is resistant to antihistamines and topical medications. Gabapentin, which is believed to act on voltage-gated N-type calcium ion channels [56], has achieved recognition as effective medication for postherpetic neuralgia [57], a common pathological condition with neuropathic pain. Since the etiology for neuropathic pain and itch seems to be basically the same, gabapentin might also be effective for neuropathic itch. Indeed, there has been a study showing effectiveness of gabapentin for brachioradial pruritus [58].

Since underlying mechanisms of pathological itch are still mostly veiled, there has been not much progress in therapeutic methods for itch. However, recent
1.13 Neurophysiology of Itch

Take Home Message

- Though the presence of itch-selective nerves responsible for histamine-induced itch has been shown, neuronal mechanisms of nonhistaminergic itch are still unclear.
- Complete suppression of skin inflammation is rather realistic than antagonizing all candidates of pruritogens in AD, considering neuronal sensitization.
- New possible medications include opioid κ-receptor agonists, antinerve growth factors substances and gabapentin.

1.13.7 Global Variations

No global variations have been reported on itch and its treatment.

References


2.1.1 Impetigo and Ecthyma

### Key Features
- Most commonly occurs in children
- Usually caused by a mixture of Staphylococcus aureus and Group AB-Hemolytic Streptococcus (GAS)
- Rarely causes hospitalization or serious complications
- Can be easily managed with oral or topical antibiotics
- Can be prevented by decreasing S. aureus skin carriage

### Etiology and Pathophysiology
Most cases of impetigo are usually caused by S. aureus, or a combination of S. aureus and GAS. It is a superficial vesiculopustular infection of the skin. Impetigo usually starts in a traumatized area of the skin. Bacteria are introduced into minor breaks in the skin and form vesiculopustules. The vesiculopustules rupture leading to a golden yellow crusting characteristic of the disease. In ecthyma, the bacterial infection extends to the dermis and causes erosions or ulcers. There is usually ulceration with crusting.

### Clinical Characteristics and Diagnosis
Impetigo presents with crusted, erythematous, 1–3 cm erosions usually on the face or extremities. There are usually multiple lesions. The lesions are usually discrete but may become confluent. Lesions are variably pruritic. In ecthyma, there are ulcerations with a thick crust. Lesions in ecthyma are more common on distal extremities, and may be tender and indurated. In both impetigo and ecthyma, there may be lymphadenopathy.

Diagnosis is usually clinical. However, if diagnosis is questionable, the following laboratory tests can be performed. These include gram stain, culture of fluid from vesiculopustules, or skin biopsy.

### General Therapeutic Outline
Treatment usually consists of topical or oral antibiotics. Debridement of the crusts is recommended with washing and gentle scrubbing. Topical antibiotics are generally used for localized disease. The best topical agent is mupirocin [1]. Oral therapy is used for multiple lesions or for patients who do not improve with topical agents. For oral therapy, it is important to cover both GAS and S. aureus, therefore penicillinase-resistant penicillins or first-generation cephalosporins are preferred. Promoting good personal hygiene through hand washing and daily bathing is also recommended to prevent spread of impetigo [2].

---

R. L. Modlin
Department of Dermatology, 52-121, UCLA School of Medicine, 10833 Le Conte Avenue, Los Angeles, CA 90024, USA
e-mail: rmodlin@mednet.ucla.edu
2.1.1.4 Current Established Therapies

Topical therapy consists of mupirocin ointment applied to lesions 3 times daily. Oral regimens include [1]:

- Dicloxacillin 250 mg p.o. 4 times daily in adults or 12 mg/kg/day in four divided doses p.o. in children
- Cephalexin 250 mg p.o. 4 times daily in adults or 25 mg/kg/day in four divided doses p.o. in children
- Erythromycin 250 mg p.o. 4 times daily in adults or 40 mg/kg/day in four divided doses p.o. in children
- Clindamycin 300–400 mg p.o. 3 times daily in adults or 10–20 mg/kg/day in three divided doses p.o. in children
- Amoxicillin/clavulanate 875/125 mg p.o. 2 times daily or 25 mg/kg/day of amoxicillin in two divided doses p.o. in children

2.1.1.5 Experimental Approaches

A recent study by Kuniyuki et al compared the effects of topical tetracycline vs. topical treatment plus oral antibiotics and found no significant difference between the two groups. This study suggests that topical tetracycline is an effective treatment for impetigo [3].

2.1.1.6 Complications to Avoid

The most well known complication of impetigo caused by nephritogenic strains of GAS is poststreptococcal glomerulonephritis. Unfortunately, there is no evidence that treatment of impetigo prevents this complication. Other complications include meningitis or sepsis in infants, erysipelas, deep cellulitis, bacteremia, osteomyelitis, septic arthritis, pneumonia, and lymphadenitis. Two rarer forms of impetigo can also occur including ecthyma and bullous impetigo. Ecthyma is an ulcerative form of impetigo caused by GAS. Bullous impetigo is a toxin-mediated erythoderma in which the epidermal layer of the skin sloughs off in large areas of skin loss. It is mediated by the same toxin (exfoliative toxin A) as seen in bullous pemphigoid [4].

2.1.1.7 Global Variations

Internationally, the epidemiology of impetigo is relatively unknown and the choice of treatment for impetigo is subject to debate. In a Dutch study evaluating the treatment of impetigo between 1987 and 2001, it was found that there was a rise in treating impetigo with topical antibiotics (43–64%) and a decrease in treating with oral antibiotics (31–14%) and antiseptics (11–3%) [5]. The incidence of impetigo increased from 16.5% in 1987 to 20.6% in 2001 [5].

2.1.2 Folliculitis, Furuncles, and Carbuncles

2.1.2.1 Etiology and Pathophysiology

Folliculitis is a pyoderma of the hair follicles. A furuncle is an inflammatory nodule of the hair follicle. A carbuncle is a series of abscesses in the subcutaneous tissue that drain via hair follicles. S. aureus is the most common cause of these lesions. In folliculitis, Pseudomonas aeruginosa is another common cause,
especially when associated with whirlpools, hot tubs, and swimming pools [6].

### 2.1.2.2 Clinical Characteristics and Diagnosis

The lesions of folliculitis are small, multiple, erythematous, cluster in groups, pruritic, and may have a central pustule at the peak of the raised lesion. Furuncles are painful nodules within the skin. Carbuncles are a deeper infection of the skin associated with fever. Carbuncles are made up of interconnected furuncles that drain pus through multiple opening of the skin.

### 2.1.2.3 General Therapeutic Outline

For folliculitis and small furuncles, moist heat can be used to promote drainage. However, for larger furuncles and all carbuncles, incision and drainage are needed. Systemic antibiotics are needed if there is surrounding cellulitis or fever. Antibacterial soaps and good personal hygiene are important factors in preventing infection. Eradication of staphylococcal carriage among colonized people is also an important means of prevention [1].

### 2.1.2.4 Current Established Therapies

For patients with furuncles or carbuncles and systemic symptoms such as fever, antimicrobial therapy is indicated. Antimicrobial therapy should be directed against *S. aureus*. Antibiotic regimens include [1]:

- **Dicloxacillin** 500 mg 4 times per day p.o. in adults or 25 mg/kg/day in four divided doses p.o. in children
- **Cephalexin** 500 mg 4 times per day p.o. in adults and 25 mg/kg/day in four divided doses p.o. in children
- **Clindamycin** 300–450 mg 3 times per day p.o. in adults or 10–20 mg/kg/day in three divided doses p.o. in children

The standard of care in the emergency room and often in the clinic is to assume that everything is MRSA until cultures prove otherwise. Due to the high prevalence of MRSA, it is important to obtain cultures and modify therapy to provide MRSA coverage. In fact, in a recent study evaluating the prevalence of MRSA among patients with skin and soft-tissue infections in emergency departments, *S. aureus* was isolated in 76% of patients, and MRSA was isolated from 59% of patients [7]. The standard treatment for MRSA skin and soft-tissue infections includes either doxycycline 100mg given orally twice daily, clindamycin 300-450 mg po every 6-8 hours (assuming there is no clindamycin resistance), or trimethoprim-sulfamethoxazole 2 double-strength tabs twice daily. Linezolid (600 mg twice per day p.o. in adults and 10 mg/kg/day every 12 h p.o. in children) is also effective [1]. For MRSA bacteremia, IV vancomycin (30 mg/kg/day in two divided i.v. doses in adults and 40 mg/kg/day in four divided i.v. doses in children) is the treatment of choice, but if contraindicated, daptomycin or linezolid may also be used.

### 2.1.2.5 Experimental Approaches

The best method for controlling folliculitis, furuncles, and carbuncles is to reduce carriage of *S. aureus*. In carriers of *S. aureus*, application of topical mupirocin to the anterior nares was found to reduce the nasal colonization with *S. aureus* and recurrence rate of folliculitis or furunculosis [8]. A single oral daily dose of clindamycin (150 mg) for 3 months has also been found to reduce infections by approximately 80% [9].

### 2.1.2.6 Complications to Avoid

Furunculosis in the nasal and perioral area can result in cavernous sinus infection. Bacteremia can also result causing significant morbidity and mortality.

---

**Take Home Message**

- Folliculitis, furuncles, and carbuncles are common soft tissue infections of the skin that can usually be easily treated and generally do not cause complications. The emergence of MRSA however, has required stronger antibiotic treatment.
2.1.3 Erysipelas

### Key Features
- Usually caused by Beta-hemolytic Group A Streptococci (GAS)
- Systemic symptoms are present
- Can produce a butterfly rash on the face
- Lesions are sharply marginated, discrete and raised

#### 2.1.3.1 Etiology and Pathophysiology

Most cases of erysipelas are caused by GAS. Rarer causes include *S. aureus*, *S. pneumoniae*, enterococci, and aerobic gram negative bacilli [10]. The bacteria infect the upper dermis and cause marked swelling. Usually erysipelas occurs in areas of skin where there is trauma, allowing a portal of entry for infection. Obesity, venous stasis, and lymphedema are predisposing factors [11].

#### 2.1.3.2 Clinical Characteristics and Diagnosis

Erysipelas presents as a painful, indurated, erythematous, raised plaque that is sharply marginated from the surrounding skin. The most common sites of infection include the face and lower legs. When erysipelas occurs on the face, it can cause a butterfly distribution involving the cheeks and bridge of the nose. Lymphangitis and local lymphadenopathy may also be present. Systemic symptoms are also usually present, including malaise, fever, and chills.

Diagnosis is usually clinical. However, skin biopsy, serology for GAS, and cultures of the skin lesions may yield additional diagnostic information. Blood cultures are usually low yield [10].

#### 2.1.3.3 General Therapeutic Outline

Therapy includes an antibiotic active against both GAS and *S. aureus*.

2.1.3.4 Current Established Therapies

Oral or parenteral penicillin is the treatment of choice [1]. However, if *S. aureus* is suspected, a pencillinase-resistant penicillin or first-generation cephalosporin should be used [12]. Roxithromycin has also been found to be as effective as penicillin [13].

#### 2.1.3.5 Experimental Approaches

In a single randomized, double-blind, placebo-controlled trial, the addition of systemic corticosteroids to antibiotics in patients diagnosed with erysipelas had a positive outcome. Specifically, median healing time, median duration of hospital stay, and median treatment time with intravenous antibiotics were all shortened by 1 day in patients treated with prednisolone vs. patients treated with placebo [14].

#### 2.1.3.6 Complications to Avoid

Include recurrent erysipelas, bacteremia, metastatic abscess formation, infective endocarditis, meningitis, osteomyelitis, septic arthritis, and streptococcal toxic shock syndrome.

### Take Home Message
- Erysipelas is an infection of the upper dermis that has an excellent prognosis with proper diagnosis and treatment. However, serious complications can occur if treatment is delayed and infection spreads to the deeper tissues.

2.1.4 Cellulitis

#### Key Features
- Usually caused by GAS or *S. aureus*
- Systemic symptoms are present
- Lesions are not sharply marginated
- Infection is deeper than erysipelas
2.1.4.1 Etiology and Pathophysiology

Cellulitis is infection of the dermis and subcutaneous tissues. The most common microorganisms that invade the tissues include GAS and S. aureus. Disruption of the cutaneous barrier, venous or lymphatic compromise, or a previous history of cellulitis are all predisposing factors. The pathogenesis of how cellulitis occurs is not known. However, it is thought that bacterial exotoxins invoke a local cytokine release resulting in the clinical features of cellulitis [15]. The number of actually infecting organisms in cellulitis is usually quite small.

2.1.4.2 Clinical Characteristics and Diagnosis

Cellulitis has both local and systemic signs. The affected area is usually swollen, warm, tender, and erythematous. Unlike erysipelas, the area is usually not sharply defined nor raised. Lymphadenopathy, lymphangitis, and abscess formation may also be present. Systemic symptoms include fever, chills, fatigue, and myalgias.

Diagnosis is usually clinical. Cultures of the blood, skin aspirates, and skin biopsies usually do not reveal additional diagnostic information. However, if MRSA is suspected, if there is recurrent disease, or if there is no response to therapy, blood cultures may be indicated [16]. Serological studies for Streptococcus (e.g., ASO titers, Streptozyme antibody assay) can be used to support the diagnosis of streptococcal cellulitis. Plain radiographs are often used for diagnosis in severe cases. If radiographs show gas in the tissues, then surgical intervention is needed.

2.1.4.3 General Therapeutic Outline

Uncomplicated cellulitis may be treated with oral antibiotics on an outpatient basis. Complicated cellulitis may require admission to the hospital for i.v. antibiotics. Criteria for complicated cellulitis include rapidly spreading lesions, prominent systemic symptoms, or coexisting medical conditions [12].

2.1.4.4 Current Established Therapies

Initial treatment includes intravenous antibiotics including [12]:
- Nafcillin 1.0–1.5 g i.v. every 4–6 h
- Ceftriaxone 1.0 g i.v. every 24 h
- Cefazolin 1.0 g i.v. every 6–8 h

Subsequent treatment includes:
- Dicloxacillin 0.5 g p.o. every 6 h
- Cephradine 0.5 g p.o. every 6 h
- Cephalexin 0.5 g p.o. every 6 h
- Cefadrozil 0.5 g p.o. every 6 h

Initial treatment if MRSA is suspected or the patient is penicillin allergic:
- Vancomycin 1.0–2.0 g i.v. every 24 h
- Linezolid 0.6 g i.v. every 12 h

Subsequent treatment:
- Linezolid 0.6 g i.v. every 12 h

Treatment should be switched to oral medication once systemic symptoms resolve and skin findings resolve. Total treatment time should be 7–14 days.

2.1.4.5 Experimental Approaches

Recurrence is a common complication of cellulitis. Therefore, the use of monthly intramuscular injections of benzathine penicillin G to prevent recurrence of cellulitis was evaluated. It was found that prophylaxis reduced the recurrence rate to zero among patients without predisposing factors to cellulitis (such as diabetes mellitus, obesity, liver cirrhosis, and CHF) but failed to prevent recurrence in those with predisposing factors (20%). Therefore, daily prophylaxis with oral penicillin G should be considered in patients with recurrent cellulitis without predisposing factors [17].

2.1.4.6 Complications to Avoid

Include recurrent cellulitis, local abscess, superinfection, lymphangitis, gangrene (gas-forming gangrene), bacteremia, and sepsis.
2.1.4.7 Global Variations

Treatment strategies are similar in the United States and Europe. In a retrospective review of all cases of erysipelas and cellulitis in a tertiary care center in Italy from 1995 to 2002, the most commonly used antibiotic was amoxicillin–clavulanic acid. The most used antibiotic combinations were beta-lactams plus lincosamides, quinolones plus lincosamides, and penicillinase-resistant penicillins plus other antibiotics. No significant differences were found between the different treatment groups [18].

2.1.5 Necrotizing Fasciitis

2.1.5.1 Etiology and Pathophysiology

There are two types of necrotizing fasciitis. Type I is caused by a mixed infection with aerobic and anaerobic bacteria. Common bacteria include S. aureus, streptococci, enterococci, E. coli, peptostreptococcus, prevotella, bacteriodes, and clostridium [19]. It most commonly occurs in diabetics, obese patients, patients who are immunosuppressed, and patients who have had surgical procedures. Type II is caused by GAS. It can occur in any age range and in patients with no previous medical illnesses. Risk factors for type II necrotizing fasciitis include blunt trauma, chicken pox, i.v. drug abuse, childbirth, and surgical procedures. In both types, there is rapid progression of infection with extensive necrosis of subcutaneous tissues, thrombosis of blood vessels, and spread of bacteria along fascial planes. Infection often begins at the site of nonpenetrating minor trauma. Bacteria reach the site from transient bacteremia, local seeding, or penetrating injury. Within 36–72 h of infection, characteristic findings usually appear, including erythema and vesicles or bullae containing yellow to reddish-black fluid. The bullae rupture leaving denuded skin and a black eschar forms which sloughs off by 7–10 days. Mortality rate is high, 21% in type I necrotizing fasciitis [20] and 30–34% in type II necrotizing fasciitis [21].

2.1.5.2 Clinical Characteristics and Diagnosis

An accurate diagnosis can only be surgically and pathologically made. However, unexplained pain, erythema, bullae formation, fever, malaise, myalgias, and hypotension are all clinical characteristics of the disease. Unexplained pain may be the first manifestation and is especially important to look for in high risk patients [22]. In type I, necrotizing fasciitis occurs most commonly in the feet, head and neck, and perineum.

2.1.5.3 General Therapeutic Outline

Treatment consists of surgical exploration and debridement of necrotic tissue, antibiotic therapy, and supportive care. The earlier the surgical intervention is performed, the better the prognosis.

2.1.5.4 Current Established Therapies

The goals of the initial surgery are to establish a diagnosis, and to remove all necrotic tissue found. Repeat surgeries should be performed every 24 h to repeat exploration and debridement until all necrotic tissue is removed. Antibiotic therapy depends on the type of organism involved. Since many kinds of bacteria are
involved in type I necrotizing fasciitis, cultures and sensitivities should be obtained. Empirical treatment should cover both aerobes and anaerobes. Once culture results are obtained, antibiotics should be changed accordingly. For type I infection, the following agents are recommended [1]:

- Ampicillin-sulbactam 1.5–3.0 g every 6–8 h OR Piperacillin-tazobactam 3.37 g every 6–8 h i.v.
- Clindamycin 600–900 mg/kg every 8 h i.v.
- Ciprofloxacin 400 mg every 12 h i.v.
- Imipenem/cilastatin 1 g every 6–8 h i.v.
- Meropenem 1 g every 8 h i.v.
- Ertapenem 1 g every day i.v.
- Cefotaxime 2 g every 6 h i.v.
- Metronidazole 500 mg every 6 h i.v.
- Clindamycin 600–900 mg/kg every 8 h i.v.

Since type II necrotizing fasciitis is overwhelmingly caused by GAS, penicillin G is commonly used. However, many studies have found clindamycin superior to penicillin in necrotizing fasciitis [23, 24]. Therefore, both penicillin and clindamycin are recommended [1]:

- Penicillin 2–4 MU every 4–6 h i.v.
- Clindamycin 600–900 mg/kg every 8 h i.v.

### 2.1.5.5 Experimental Approaches

Intravenous immunoglobulin (IVIG) is a controversial therapy for toxic shock syndrome. Although there is no conclusive data that supports the use of IVIG therapy, there are some studies that support its use. In a recent study, seven patients with severe GAS soft tissue infection were treated with antimicrobials and high-dose IVIG. Immunostaining of the patients who had high levels of GAS, superantigen, and pro-inflammatory cytokines initially, had dramatically reduced levels post-IVIG therapy, suggesting that IVIG therapy may be an effective adjuvant therapy in the treatment of GAS necrotizing fasciitis, and limit the need for surgical debridement [25]. Although some studies show promise of IVIG as an efficacious therapy, additional studies need to be done to further support its use.

### 2.1.5.6 Complications to Avoid

Bacteremia, sepsis and death.

### Take Home Message

- Necrotizing fasciitis is a rare subcutaneous infection that can occur in both healthy and immunocompromised patients. It causes devastating tissue destruction and has a high morbidity and mortality rate. Therefore, diagnosis needs to be made rapidly. Treatment includes a combination of antibiotics and surgical debridement. IVIG is also a possible treatment, although there is not enough evidence yet to recommend its use.

### 2.1.5.7 Global Variations

The incidence of severe invasive infections caused by GAS has been increasing in many countries. In the US, a survey conducted between 1995 and 1999 in five US states found that the rate of invasive GAS was 3.5 cases per 100,000 persons [26]. Also, in an Ontario based study conducted between 1991 and 1995, the incidence of group A streptococcal necrotizing fasciitis was between 0.085 and 0.40 per 100,000 population [21].

### 2.1.6 Staphylococcal Scalded Skin Syndrome

#### Key Features

- Most common in infants and children less than 5 years
- Can occur in adults, in whom mortality rate is much higher
- Exotoxin mediated
- Causes generalized epidermal sloughing
- Usually treated with oral or intravenous antibiotics
2.1.6.1 Etiology and Pathophysiology

Staphylococcal scalded skin syndrome (SSSS) is caused by certain strains of Staphylococci producing an epidermolytic toxin. The most common type is *S. aureus* of phage group 2 (types 71 and 55), which produces exfoliative toxins A and B.

The bacteria usually colonize superficial areas of the skin, including the nasopharynx or conjunctiva; SSSS usually begins from a distant focus of staphylococcal infection. From the focus of infection, the bacteria release exfoliative toxins that are transported hematogenously to the skin. The exfoliative toxins cause acantholysis by specific cleavage of desmoglein 1, a desmosomal cadherin protein responsible for cell-to-cell adhesion of keratinocytes, within the stratum granulosum of the epidermis.

2.1.6.2 Clinical Characteristics and Diagnosis

The presenting symptoms include fever, malaise, and a generalized, erythematous rash that becomes sandpaper-like. Over time, the rash becomes tender. Once epidermolysis occurs, sloughing of the superficial layer of the epidermis occurs and Nikolsky sign (slippage of the superficial layer of the epidermis with gentle pressure) is present. Desquamation leaves the underlying skin with a red, moist base. The skin heals in approximately 2 weeks and does not cause scarring.

Diagnosis is usually clinical; however, definitive diagnosis depends on culture and biopsy results. Cultures may be obtained from the conjunctiva, nasopharynx, or foci of bacterial skin infection. Biopsy of frozen sections of the lesions from SSSS will reveal intraepidermal cleavage within the stratum corneum with no inflammatory cells in the epidermis or dermis. ELISA or immunodiffusion assays may be used to identify the exfoliative toxin of SSSS.

2.1.6.3 General Therapeutic Outline

Therapy consists of antibiotics, supportive care, and managing fluid and electrolytes. Oral antibiotics are required for eradication of *S. aureus*. Topical antibiotics are ineffective [27].

2.1.6.4 Current Established Therapies

Oral penicillinase-resistant antibiotics such as cloxacillin or dicloxacillin can be used. First-line systemic therapy is oral or intravenous flucloxacillin [28]. It is also important to swab the skin and obtain nasal swabs from the patient and immediate contacts to identify the primary source of infection, for bacteriological confirmation and antibiotic sensitivities, and to identify asymptomatic nasal carriers of *S. aureus* [28].

2.1.6.5 Experimental Approaches

Currently, research is being conducted to elucidate the mechanism of action of exfoliative toxins. Discovering the mechanism of action of these toxins may lead to the development of effective antitoxins. These antitoxins may decrease the extent of exfoliation in severe cases, as may occur in late presentation or delayed diagnosis of the disease, in antibiotic resistant strains, and in patients where mortality rates are high.

2.1.6.6 Complications to Avoid

Include cellulitis, sepsis and pneumonia; if disease is extensive enough, death can occur. Whereas mortality in childhood SSSS is approximately 4%, the mortality rate in adults is reported to be greater than 60% [29].

Take Home Message

- SSSS is a common disease that is usually easily diagnosed on clinical grounds and treated with conventional antibiotics. Complications are usually rare yet the mortality rate is unacceptably high. Research into developing an effective antitoxin is still currently needed.
2.1.6.7 Global Variations

There is little epidemiological data on the annual incidence of SSSS infections. However, SSSS tends to occur in outbreaks. In one epidemiological study on the rate of SSSS in Germany it was found that the annual incidence of SSSS was between 0.09 and 1.13 cases per one million inhabitants [30].

2.1.7 Cutaneous Anthrax

Key Features

- Caused by spore forming bacteria
- Exotoxins cause local edema and necrosis of skin
- Lesion causes a black eschar that is not painful
- Usually no systemic signs
- Recent bioterrorism agent

2.1.7.1 Etiology and Pathophysiology

Cutaneous anthrax is caused by the spore-forming gram positive rod *Bacillus anthracis*. Spores can be found in any soil rich in organic matter. Infection with anthrax requires three exotoxins: edema factor, lethal factor, and protective antigen. Protective antigen binds to a cell surface receptor and enables the binding of edema factor or lethal factor [31]. Edema factor is an adenyl cyclase that impairs host defenses. Lethal factor is a protease that causes lysis of macrophages [32]. Together, these exotoxins cause edema and tissue necrosis when the spore of *B. anthracis* is introduced in the skin.

2.1.7.2 Clinical Characteristics and Diagnosis

Cutaneous anthrax presents as a painless, pruritic papule that occurs 3–5 days after inoculation. The papule then forms a vesicle and undergoes central necrosis, leaving a black eschar surrounded by edema. There may also be purplish vesicular satellite lesions extending proximally from the eschar. There are usually no systemic signs such as fever, unless secondary infection of the lesion occurs. Edema is more extensive on the head and neck region.

The diagnosis of cutaneous anthrax is made by obtaining gram stain and culture of the skin lesion, obtaining blood cultures, getting a punch biopsy of the skin lesion if cultures are negative despite high suspicion of infection, and notifying local public health authorities. There are also many new diagnostic tests for anthrax including enzyme linked immunosorbent assay and polymerase chain reaction.

2.1.7.3 General Therapeutic Outline

Although cutaneous anthrax lesions can resolve without complications, antibiotic treatment is recommended. Although penicillin is usually an effective therapy, ciprofloxacin is the recommended drug of choice for the treatment of anthrax until culture and sensitivities are available, due to the possibility of genetically altered *B. anthracis*.

2.1.7.4 Current Established Therapies [33]

The CDC guidelines for the treatment of cutaneous anthrax include ciprofloxacin and doxycycline as first-line therapy. The recommended doses are the following:

- Ciprofloxacin 500 mg twice a day
- Doxycycline 100 mg twice a day

For naturally acquired cutaneous anthrax, the recommended treatment duration is 7–10 days. Disease resulting from a potential terrorist attack should be treated for at least 60 days to protect against late germinating spores potentially causing systemic anthrax. It is also recommended that corticosteroids be used in cases with extensive edema or swelling in the head and neck region.
2.1.7.5 Experimental Approaches

Though the first vaccine against anthrax was developed in 1954 [34] it has gone through major improvements since then. Today, the only vaccine approved for use in the United States is the anthrax vaccine adsorbed (AVA), which contains a cell-free filtrate of cellular products including lethal factor, edema factor, and protective antigen that is adsorbed to aluminum hydroxide as an adjuvant. The vaccine is highly efficacious, producing seroconversion with a fourfold rise in anti-PA IgG titers after three doses in 95% of vaccines [35]. Currently, the vaccine is recommended in people that work with high concentrations of B. anthracis cultures, people involved in activities with a high potential for aerosol production, and military personnel with a risk for exposure to anthrax [36]. However, the recent terrorist attacks using spores of B. anthracis have stimulated interest in developing new vaccines for anthrax prevention. A recombinant vaccine with a lower risk of reactogenicity as well as alternate vaccine delivery routes are underway [37].

2.1.7.6 Complications to Avoid

Systemic dissemination, microangiopathic hemolytic anemia and coagulopathy, malignant edema of the head and neck interfering with respiration, septicemia resulting in toxic shock and death.

2.1.7.7 Global Variations

Anti-anthrax serum has been used in China and the Russian federation as a means of therapy when treatment is delayed and antibiotics may be too late. The hyperimmune serum therapy containing antitoxin antibodies can be life-saving in pulmonary, intestinal, or complicated cutaneous cases of anthrax where treatment has been delayed and circulating levels of toxin are high [38].

The estimated worldwide incidence of anthrax in 1958 was between 20,000 and 100,000 cases annually [39]. The incidence may be considerably lower today; however, the true frequency of the disease is unknown. In the United States, prior to the recent bioterrorism attacks in 2001, the incidence of anthrax was less than one case annually over the past two decades [40]. Most of the US cases in recent decades have resulted from bioterrorism or exposure to wool or animal hair.

2.1.8 Leprosy

2.1.8.1 Etiology and Pathophysiology

Leprosy is a chronic granulomatous disease caused by M. leprae. M. leprae is an obligate intracellular acid-fast bacillus that grows best in cooler temperatures. Therefore, infection primarily takes place in the cooler tissues of the body including the skin, peripheral nerves, anterior chamber of the eye, upper respiratory tract, and testes. The definitive route of transmission for leprosy is unknown; however the disease is most likely spread by the respiratory route or through broken skin. Once the respiratory tract is infected, widespread dissemination occurs.
Once primary infection occurs, there is a clinical spectrum of leprosy infection that correlates with the level of the immune response to the pathogen. In individuals with the tuberculoid form (TT), the immune response is characterized by cell-mediated immunity with the expression of $T_h^1$ cytokines, including interleukin-2 and interferon-gamma. On the other pole of the disease, individuals have a lepromatous form (LL). In LL, there is a humoral response, with the expression of $T_h^2$ cytokines, including interleukin-4, interleukin-5, and interleukin-10. The spectrum of disease between TT and LL depends on the ability of the immune system to upgrade toward the cell-mediated immune reaction, and is characterized by the reduction of bacilli in lesions and the influx of TH1 cells into disease lesions. These types include indeterminate (I), borderline tuberculoid (BT), mid-borderline (BB), and borderline lepromatous (BL) forms. Reactions occur when there is a shift in the immune response to leprosy. These shifts can result in delayed type hypersensitivity reactions (termed reversal or Type 1 reactions), humoral hypersensitivity reaction with immune complex deposition (termed erythema nodosum leprosy or type II reactions), and Lucio reactions, a variant of type II reactions. These reactions are often associated with additional neurological loss if not promptly treated.

### 2.1.8.2 Clinical Characteristics and Diagnosis

The clinical characteristics of the disease depend on the form of leprosy and degree of cell-mediated immunity to *M. leprae*. The onset of the disease is insidious with incubation time generally between 5 and 7 years. Infection first affects the peripheral nervous system resulting in painful parasthesias and numbness. Next, there is skin infection which can result in anything from just a few, small macules to large, coalescing nodules. Nose involvement can result in chronic nasal congestion to destruction of cartilage and resulting deformity. Eye involvement can result in cranial nerve palsies, uveitis, glaucoma, cataracts, and corneal damage. The testes may also become infected resulting in hypogonadism. In the extremities, there can be sensory neuropathy, nerve palsies, contractures, and ulceration. Laryngeal involvement may result in hoarseness. There can also be a loss of eyebrows and lashes. Generally, in tuberculoid leprosy, symptoms are less severe, with skin lesions characterized by a few well-defined hypopigmented to erythematous macules with diminished sensation and nerve involvement resulting in sensory and/or motor loss in the vicinity of a tuberculoid lesion. On the other hand, in lepromatous leprosy, symptoms are much more severe. Lepromatous disease is usually generalized and consists of erythematous macules, papules and/or nodules and much more extensive nerve involvement. Finally, reversal reactions are characterized by erythema and edema of pre-existing skin lesions, and can also be accompanied by neuritis and ulceration. Erythema nodosum reactions can result in painful erythematous nodules of the skin and subcutaneous tissues. Lucio reactions can result in cutaneous hemorrhagic infarcts.

Diagnosis consists of physical examination, skin smear, and/or skin biopsy. On physical examination lesions should be evaluated for enlargement, tenderness, and sensory loss. Skin smears can be taken from lesions on any affected part of the body and are evaluated using Ziehl-Neelsen staining, which stains for acid-fast bacilli. Biopsies are also taken from within the lesions, and can demonstrate the extent and type of infiltrate and involvement of dermal nerves.

### 2.1.8.3 General Therapeutic Outline

Treatment of leprosy is long and difficult to manage. General principles include eradication of infection with antilepromatous drugs, reducing the risk of nerve damage, and preventing and treating reactions.

### 2.1.8.4 Current Established Therapies

The current multidrug therapy regimen recommended by the World Health Organization is:

#### Paucibacillary leprosy (five lesions or fewer):
- Dapsone (100 mg daily) and rifampicin (600 mg monthly) for 6 months

#### Multibacillary leprosy (more than five lesions):
- Dapsone (100 mg daily), clofazimine (50 mg daily), rifampicin (600 mg monthly) and clofazimine (300 mg monthly) for 24 months
2.1.8.5 Experimental Approaches

There have been many new drugs developed against \textit{M. leprae}; these include fluoroquinolones, cyclines and macrolides. As a result of a double-blind, control, clinical trial, the Seventh Report of the WHO Expert Committee on Leprosy recommended in 1997, the use of single-dose of a combination of rifampicin, ofloxacin, and minocycline as an acceptable and cost-effective alternative regimen for the treatment of single-lesion paucibacillary leprosy [44]. They also concluded that the duration of the current standard regimen for multibacillary leprosy could be shortened to 12 months. Various immunotherapeutic agents (vaccines and cytokines) are also being studied as an adjunct to therapy for multibacillary leprosy. Recently, it has been found that immunotherapy with the Bacillus Calmette-Guerin (BCG) and \textit{Mycobacterium welchi} vaccines can be a useful adjunct to the current standard regimen for multibacillary leprosy to decrease the risk of reactions and relapses in highly bacilliferous BL/LL patients [45].

2.1.8.6 Complications to Avoid

Complications include injury due to neurological deficits, secondary amyloidosis with renal failure, and reactional states (type 1, type 2 and Lucio’s reaction) resulting in permanent nerve injury.

2.1.8.7 Global Variations

Despite intense effort to eliminate leprosy as a public health problem, leprosy will not be eradicated in the foreseeable future. As of the beginning of 2006, the global prevalence of leprosy was 219,826 cases. The six countries with the highest rate of endemic leprosy were Brazil, Democratic Republic of Congo, Madagascar, Mozambique, Nepal and the United Republic of Tanzania. These countries account for over 24% of all cases in 2006 [46].

As for global treatment of leprosy, it seems most countries report that treatment with recommended WHO-multidrug therapy is highly effective and well tolerated. In fact, since the WHO recommendations were made in 1982, over 11.2 million patients have received it [47]. As for the newer recommendations for a single-dose of a combination of rifampicin, ofloxacin, and minocycline for the treatment of single-lesion paucibacillary leprosy, a large study from India found this regimen to be less efficacious than the standard paucibacillary-multiple drug therapy regimen, given for 6 months [48].

2.1.9 Cutaneous Tuberculosis

2.1.9.1 Etiology and Pathophysiology

Cutaneous tuberculosis is caused by infection with \textit{Mycobacterium tuberculosis}. The typical tuberculosis lesion is an epithelioid granuloma with central caseous necrosis. There are many cutaneous forms of tuberculosis. These include primary inoculation tuberculosis (PIT), tuberculosis verrucosa cutis (TVC), lupus vulgaris (LV), scrofuloderma (SD), metastatic tuberculosis abscess (MTA), acute miliary tuberculosis (AMT), and orificial tuberculosis (OT). PIT and TVC both occur through exogenous infection. In PIT, inoculation of TB on minor breaks of the skin occurs in people without immunity to TB, resulting in a tuberous chancre. In TVC, inoculation also occurs through minor breaks of the skin, but in individuals with prior TB infection. LV, SD, MTA, AMT, and OT, all occur...
through endogenous spread. LV occurs through lymphatic spread to the skin. SD occurs through lymphadenitis or tuberculosis of the joints with spread to the skin. MTA, AMT and OT all occur through hematogenous spread of TB to the skin.

### 2.1.9.2 Clinical Characteristics and Diagnosis

The clinical lesions of cutaneous TB depend on the route of infection and whether or not the infection occurred in an individual already infected with TB. In PIT, a papule develops at the site of inoculation and enlarges into a painless ulcer. Regional lymphadenopathy is also present. In TVC, there are small, red papular nodules in the skin, which evolve into verrucous plaque-like lesions. Lymphadenopathy is not present. LV presents as reddish-brown plaques (Fig. 2.1.1) typically on the head and neck. SD consists of firm subcutaneous nodules that evolve into deeper nodes or plaques that eventually perforate and discharge pus or caseous material. MTA consists of subcutaneous abscesses that coalesce, break down, and form fistulas and ulcers. In AMT, all parts of the body are affected and with disseminated crops of macules, papules, and vesicles that can become necrotic and crusted. OT consists of red papules that evolve into painful, punched-out, shallow ulcers. OT can affect the tongue, hard and soft palate, perianal skin, vulva, and glans penis.

Diagnosis consists of history, physical examination, skin biopsy, culture for acid-fast bacilli, PCR amplification of tissue specimens, and intradermal skin testing (PPD). PPD is generally positive only for PIT, LV and TVC.

### 2.1.9.3 General Therapeutic Outline

Treatment for PIT and TVC does not require systemic therapy as these forms are limited to the skin. PIT generally resolves without treatment by 1 year. TVC also can resolve without any treatment, but can persist for several years. Treatment regimens for cutaneous tuberculosis secondary to disseminated systemic infection (LV, SD, MTA, AMT, and OT) require systemic therapy. Surgical removal, electrosurgery, and cryotherapy can also be used for the hypertrophic and verrucous lesions of LV and TVC.

### 2.1.9.4 Current Established Therapies

Treatment of cutaneous tuberculosis is the same as that for pulmonary tuberculosis. Multidrug treatment is used due to the increased drug resistance among TB isolates. The current recommendations for treatment of tuberculosis includes isoniazid, rifampicin, pyrazinamide, and ethambutol daily or 3 times per week for 2 months in the initial phase. This is followed by isoniazid and rifampicin daily or 3 times per week for 4 months in the continuation phase [49]:

- Isoniazid 5 mg/kg daily or 10 mg/kg three times per week
- Rifampicin 10 mg/kg daily or 10 mg/kg three times per week
Cutaneous infections can be caused by *Bartonella henselae* and *Bartonella quintana*. Clinical disease depends on the immune status of the patient. Two cutaneous disease states include Cat-scratch disease and Bacillary Angiomatosis. Antimicrobial therapy with macrolides is generally effective.

**2.1.9.5 Experimental Approaches**

Second-line antituberculosis therapy drugs are reserved for the treatment of tuberculosis in special situations where there is drug intolerance, or resistance to first-line therapy. These include cycloserine, ethionamide, levofloxacin, moxifloxacin, gatifloxacin, paraaminosalicylic acid, amikacin, kanamycin, and capreomycin. Of the fluoroquinolones, moxifloxacin and gatifloxacin have the most activity against *M. tuberculosis* [50]. Also, newer rifamycins, such as rifabutin and rifapentine have been used. Rifabutin has the advantage of not inducing cytochrome P450 CYP3A enzymes as much as rifampin [51]. Rifapentine has the advantage of being a long-acting rifamycin with a half-life of approximately 12 h in patients [52].

**2.1.9.6 Complications to Avoid**

Recurrent or persistent infection, scarring.

**2.1.7 Global Variations**

Although the incidence of tuberculosis remains extremely high throughout the world, the incidence of global cutaneous TB appears low. Even in areas such as India where the incidence of tuberculosis is high, the incidence of cutaneous tuberculosis was only 0.15% [53]. Similarly, in a 10-year (1993–2002) retrospective study of patients seen in dermatology clinics in Hong Kong, the detected incidence of cutaneous TB among patients was only 0.04% [54].

Even though the WHO guidelines for treatment for tuberculosis have been established for pulmonary tuberculosis, currently there are no recommendations for cutaneous tuberculosis [55]. Therefore different regimens have been established globally for treatment of cutaneous TB. In India, a recent study evaluated the effectiveness of a 9-month two drug regimen. This study found that clinical resolution of cutaneous TB could be achieved even with a two drug regimen, even if drug resistance was encountered [56].

**2.1.10 Bartonella Infections**

Infection with Bartonella species produces a wide variety of clinical syndromes. Two clinical syndromes caused by Bartonella that can result in cutaneous manifestations include cat-scratch disease (caused by *B. henselae*) and bacillary angiomatosis (caused by *B. quintana* and *B. henselae*).
Cat-scratch disease is a self-limited infection that occurs after contact with a cat. It results in a primary skin or conjunctival lesion followed by regional lymphadenopathy. \textit{B. henselae} transmission from cats to humans occurs indirectly by the cat flea \textit{Ctenocephalides felis} or directly by cat scratch or bite [57]. The pathologic response to \textit{B. henselae} is a granulomatous and suppurative inflammatory reaction that is generally self-limited [58]. On the other hand, in bacillary angiomatosis, \textit{B. quintana} and \textit{B. henselae} infection of immunocompromised hosts produces cutaneous vascular proliferative disease that can cause significant mortality and morbidity if not treated.

2.1.10.2 Clinical Characteristics and Diagnosis

Cat-scratch disease is characterized by a cutaneous lesion at the site of inoculation, which develops 3–10 days after the introduction of the organism into the skin and generally evolves through vesicular, erythematous, and papular phases. The primary inoculation lesion typically persists for 1–3 weeks. Tender lymphadenopathy appears proximal to the inoculation site usually 2 weeks later, and resolves by 1–4 months. In bacillary angiomatosis, lesions typically start as reddish-purple papules that expand into large pedunculated nodules. The lesions have a vascular appearance, and are usually solitary or several in number.

2.1.10.3 Diagnosis

Diagnosis of Bartonella infection can be made using blood or tissue culture, histopathology, Wharthin-Starry silver staining, PCR, and serological methods including indirect fluorescence assay and enzyme immunosorbent assay.

2.1.10.4 General Therapeutic Outline

In cat-scratch disease, antimicrobial therapy is not required as the disease is usually self-limited. In bacillary angiomatosis, antimicrobial therapy is required. Macrolides are an effective treatment for both cat-scratch disease and bacillary angiomatosis.

2.1.10.5 Current Established Therapies

For cat-scratch disease, a 5-day course of azithromycin is recommended [59]:
- Azithromycin 500 mg on day 1, followed by 250 mg for 4 days
- For children, azithromycin 10 mg/kg orally on day 1, followed by 5 mg/kg on days 2–5

For bacillary angiomatosis, the antibiotic of choice is erythromycin, but i.v. administration should be used in patients with severe disease. Second line therapy includes doxycycline. Azithromycin and clarithromycin are newer therapies. Combination therapy, with the addition of rifampin to either erythromycin or doxycycline, is recommended for immunocompromised patients with acute, life-threatening \textit{Bartonella} infection. The combination of doxycycline and rifampin is preferred for the treatment of patients with CNS \textit{Bartonella} infection because of the superior CNS penetration of doxycycline compared with those of the other first-line antibiotics [60].
- Erythromycin p.o. 500 mg four times daily for 3 months
- Doxycycline 100 mg p.o. or i.v. twice daily for 3 months

2.1.10.6 Experimental Approaches

Neuroretinitis is a complication of cat-scratch disease in which nerve fiber layer hemorrhages, cotton-wool spots, multiple discrete lesions in the deep retina, and stellate macular exudates can occur. A retrospective case series found that patients receiving oral doxycycline 100 mg and rifampin 300 mg twice daily for 4–6 weeks had better improved resolution
of neuroretinitis, restoration of visual acuity, and clearance of bacteremia. This study demonstrates that treatment with doxycycline and rifampin in neuroretinitis may promote a shorter course of disease and better visual recovery [61].

### 2.1.10.7 Complications to Avoid

Cat-scratch disease complications include persistent fever and suppurative lymphadenitis. In bacillary angiomatosis, the disease can spread hematogenously or via lymphatics to the heart, liver, spleen, bone marrow, lymph nodes, muscles, soft tissues and CNS. Complications include endocarditis, liver abscesses, necrotizing scleritis, neuroretinitis, brain abscesses, aseptic meningitis, and encephalopathy [62–64].

### 2.1.11 Tularemia

**Key Features**

- Types of disease include ulceroglandular, glandular, oropharyngeal, oculoglandular, typhoidal and respiratory forms
- Two major subspecies of *Francisella tularenis* include Type A, which is highly virulent, and Type B, which is less virulent
- Risk factors for infection include contact with animals and insect bites
- Cell-mediated immunity is required in eliminating infection with *F. tularensis*
- Disease can produce mild to severe symptoms

#### 2.1.11.1 Etiology and Pathophysiology

Tularemia is a zoonotic disease caused by the facultative intracellular bacterium *F. tularensis*. The main vectors for transmission include rabbits, small rodents, and ticks [67]. Invasion occurs through abrasions in the skin or mucous membranes. The organisms then spread to regional lymph nodes and form granulomas and caseous necrosis. Further lymphatic and hematogeneous spread can result in septicemia and dissemination to the bone marrow, spleen and liver [68]. Since *F. tularensis* is an intracellular bacterium, it can escape the humoral response by entering macrophages without triggering the respiratory burst [69]. Therefore, cell-mediated immunity is crucial in elimination of the infection.

#### 2.1.11.2 Clinical Characteristics and Diagnosis

The clinical characteristics of tularemia depend on the subspecies involved and the route of transmission. The types of tularemia include ulceroglandular, glandular, oropharyngeal, oculoglandular, typhoidal and respiratory. Ulceroglandular tularemia is characterized by a small papule at the site of inoculation, which slowly develops into a crusting ulcer. Regional lymphadenopathy also occurs next to the site of inoculation, which can suppurate if not treated with antibiotics. Glandular
tularemia resembles the ulceroglandular form, except that there is no visible primary lesion. Oropharyngeal tularemia presents with an ulcerative tonsillitis or pharyngitis. In oculoglandular tularemia, the primary lesion occurs in the conjunctiva. Typhoidal tularemia presents with prolonged high-grade fever and bradycardia. Respiratory tularemia can cause severe respiratory distress and necrotizing pneumonitis.

The diagnosis of tularemia is based on a thorough history and physical examination. The history should include animal and insect exposure. The gold standard for diagnosis of tularemia is serology. Confirmatory testing includes serology demonstrating a fourfold rise in acute and convalescent $F. tularensis$ antibody titers. Culture is not recommended, as there is a high risk of laboratory infection. PCR tests have also been developed that have high specificity and sensitivity [70].

### 2.11.3 General Therapeutic Outline

Antibiotic therapy is the current treatment for tularemia. Prevention is also important in limiting infection. Protective gloves should be worn when handling wild animals. Protective clothing and insect repellants can aid in preventing infection by insects. A tularemia live vaccine has been developed and used in the former Soviet Union [71]. However, because it does not confer complete protection and is a live attenuated vaccine, it is not commercially available in the United States.

### 2.11.4 Current Established Therapies

Streptomycin is the antibiotic of choice for treatment of tularemia. It has a cure rate of 97% [72]. Gentamicin is another acceptable alternative. Recommended dosing in adults is:

- Streptomycin 10 mg/kg i.m. every 12 h for 7–10 days

### 2.11.5 Experimental Approaches

Although a live vaccine strain (LVS) vaccine for tularemia is being used, there are several significant problems with the vaccine. These include the fact that the basis of attenuation and protection are unknown, the strain retains virulence for mice, and there are two phenotypic variants produced when cultured. Therefore, a new vaccine is now underway. Currently, there is a search for potential sub-units and attenuation targets of $F. tularensis$ to develop a new vaccine [73].

### 2.11.6 Complications to Avoid

Complications that can occur include spontaneous drainage of suppurative lymph nodes in ulceroglandular or glandular tularemia. In typhoidal or respiratory tularemia, pericarditis, meningitis, acute respiratory distress syndrome, and rhabdomyolysis can occur.

### 2.11.7 Global Variations

Tularemia is a global disease. In the United States, there have been cases reported from every state except Hawaii. The majority of cases in the United States, however, occur in Arkansas, Missouri, and Oklahoma. Tularemia in the US is caused by the subspecies $F. tularensis$ Type A, a highly virulent species [74]. During the last 60 years, the number of cases recorded in the US has declined from 2,000 to 100 cases per year [75]. Among European countries, tularemia is also widespread. The only exceptions are the British Isles, Iceland, and Portugal. In Europe and Asia, tularemia is caused by $F. tularensis$ type B, a much less virulent subspecies [74]. The largest outbreak of
tularemia described occurred in the Soviet Union during World War II, which comprised more than 100,000 cases each year [76]. In Sweden, where the disease is endemic, there have been over 6,000 cases reported so far [77].

Treatment for tularemia depends on the type of species involved. Aminoglycosides, such as streptomycin, are the treatment of choice for Type A strains, which are found in the United States [72]. However, for Type B strains found in Europe, doxycycline is the preferred drug in most cases [74]. Treatment of Type B strains with ciprofloxacin and levofloxacin has also been efficacious [78, 79].

Acknowledgement  We are grateful to Jonathan Cotliar, M.D. for his helpful discussion.

References

76. Pollitzer R (1967) History and incidence of tularemia in the Soviet Union: a review. The Institute of Contemporary Russian studies. Fordham University, Bronx, NY
2.2 Fungal Infection

Takashi Mochizuki

2.2.1 Superficial Fungal Infection

Key Features

- Superficial fungal infection is the most prevalent skin disease.
- Detection of the pathogen from a lesion by mycological tests is essentially important.
- Superficial infections are usually successfully treated with topical antimycotics.
- Onychomycoses and hair infections require oral antimycotics.

2.2.1.1 Dermatophytosis

2.2.1.1.1 Etiology and Pathophysiology

A variety of predominant etiologic agents of tinea capitis (scalp ringworm) has been widely known for a long time [1]. *Micorsporum (M.) canis*, a zoophilic dermatophyte, is the most predominant agent among children. *Trichophyton (T.) tonsurans* has also been reported as a major causative agent among school children. This species is known to have caused a worldwide epidemic of tinea among active players of high-contact sports such as judo and wrestling [2, 3]. Among the elderly, epidemics of *T. violaceum* have been reported in Eastern Europe [1] and Japan [4].

The common causative agents of tinea corporis are *T. rubrum, M. canis, T. mentagrophytes*, and *T. tonsurans*. Widespread tinea corporis may reflect an underlying immunodeficiency. Multiple small lesions on exposure regions may be caused by *M. canis*. Zoophilic *T. mentagrophytes*, and *T. verrucosum* may produce highly inflammatory lesions.

Feet are the portal of the dermatophyte infection, and tinea pedis is the most common dermatophytosis. Tinea pedis also plays the role of a major reservoir of fungi. The most common agent is *T. rubrum*, followed by *T. mentagrophytes* (var. *interdigitale*), both of which are known to be typical anthropophilic species.

The major causative agents of onychomycosis are dermatophytes, especially *T. rubrum* and *T. mentagrophytes* (var. *interdigitale*). Other nondermatophyte species such as *Candida* sp. [5], *Scopulariopsis, Acremonium*, and *Fusarium* sp. [6, 7] produce similar lesions.

2.2.1.1.2 Clinical Features

Tinea capitis: The lesions show seborrhic dermatitis-like eruptions, with breakdown of hair, and occasionally cause severe inflammation referred to as kerion. *Trichophyton tonsurans* present as hair disruption at the surface of the skin, leaving the appearance of black dots composed of follicle openings filled with degraded hair (black dot ringworm).

Tinea corporis and tinea cruris: Clearly demarcated scaly erythema with central healing produces annular outlines (ringworm) (Fig. 2.2.1). Tinea lesions on the face (tinea faciei) often lack this annular appearance and scaly border and are frequently misdiagnosed. In males, tinea cruris rarely extends as far as the scrotum and penis shaft, but usually extends from the groin to upper thighs.

T. Mochizuki
Department of Dermatology, Kanazawa Medical University, Daigaku 1-1, Uchinada, Kahoku, Ishikawa 92-0293, Japan
E-mail: mocizuki@kanazawa-med.ac.jp
Tinea pedis and tinea manuum: The lesions are classified into three types as interdigital, vesicular, and hyperkeratotic. Hyperkeratotic type usually lacks itching and is accompanied by tinea unguium. Hands are rarely involved but when they are, they usually show diffuse hyperkeratosis or desquamation limited to one side.

Tinea unguium: Dermatophyte infection of nail plates are classified as distal and lateral subungual onychomycosis (DLSO), superficial white onychomycosis (SWO), proximal subungual onychomycosis (PSO), and total dystrophic onychomycosis (TDO).

2.2.1.1.3 Diagnosis

The diagnosis can be confirmed by potassium hydroxide (KOH) preparation and the culture of horny material, broken hair, or pulverized nail samples. The hairbrush culture method is very useful for the survey of tinea capitis and hair dermatophyte carriers [3]. For tinea unguium, histopathology using periodic acid-Schiff (PAS) stain is performed at times. It is said that less than 50% of what clinically resembles onychomycosis represents true fungal infection [2] and mycological tests are essential for the diagnosis. Onychomycoses caused by a few nondenmatophyte species, such as Candida sp., Aspergillus sp., and Fusarium sp., may resist standard therapy with terbinafine, therefore, culture-based identification of the causative agent is of importance at the beginning of systemic antimycotic therapy.

2.2.1.1.4 General Therapeutic Outlines

Tinea capitis: Topical antimiycotics are ineffective. The optimal dose or treatment period may be changed according to the causative fungal species. Griseofulvin at 10–20 mg/kg/day for 2–4 months, terbinafine at 250 mg/day for 4 weeks, or itraconazole at 5 mg/kg/day for 2–3 weeks is needed. Tinea capitis caused by M. canis and T. tonsurans requires prolonged treatment. Daily use of shampoo containing miconazole nitrate is reported to reduce the incidence of infection [8]. Mechanical epilation of infected hair from kerion lesion aids treatment.

Tinea corporis and tinea cruris: Topical antimiycotics such as azoles, ciclopirox olamine, morpholine, terbinafine, benzylamine, and thiocarbamates for 1-2 weeks is usually very effective. For exceptional cases such as extensive lesions or follicular lesions, including black dot type hair infections, oral antimiycotics are useful.

Tinea pedis and tinea manuum: Simple application of topical antimiycotics for 4 weeks is effective. Hyperkeratotic type lesions need prolonged (3 months) daily application of newly developed azoles or terbinafine. Hyperkeratotic type may be successfully treated with griseofulvin in doses of 10 mg/kg/day for 4 weeks, terbinafine at 250 mg/day for 2 weeks, or itraconazole at 5 mg/kg/day for 1–2 weeks.

Tinea unguium: Double blind, randomized studies have reported terbinafine at 250 mg/day for 12 or 16 weeks to be significantly more effective [9] and with less likelihood of relapse [10] than itraconazole at 400 mg/day for 1 week in every 4 weeks for 12 or 16 weeks. Alternatively, Fluconazole at doses of 150–300 mg once a week for 6–12 months appears to be effective. Removal (mechanical or chemical) of the abnormal nail plate appears to improve the response to systemic antimiycotic therapy [4], especially in cases with TDO, DLSO with cavity and dermatophytoma, and yellow streaks within the nail. SWO is an indication for abrasion of the superficial lesion followed by the use of topical antimiycotics. The topical management of onychomycosis has improved with the introduction of ciclopirox and amorolfine nail lacquers [4].

2.2.1.1.5 Current Established Therapies

As for shortening the term of topical treatment for tinea pedis, 1 week use of terbinafine was reported to be comparable with 4 weeks use of clotrimazole [11].
and 2 weeks use of luliconazole was reported to be comparable with 4 weeks use of bifonazole [12].

### 2.2.1.1.6 Complications to Avoid

If the lesion is extensively oozy, the skin is macerated or there is suppuration, antimycotics may be irritable and 1–2 weeks of corticosteroid and/or antibiotic ointment is needed to improve the skin condition prior to a course of antimycotics.

Prior to initiating oral terbinafine treatment, liver enzyme levels should be monitored, and a complete blood count should be obtained and repeated every 4 weeks during treatment according to the product label. Itraconazole and other azole drugs not only inhibit fungal cytochromes but also affect the hepatic cytochrome P450 system of humans, leading to drug interactions.

### 2.2.1.7 Global Variations

A half dose of terbinafine (125 mg/day) has been reported to be as effective as 250 mg/day in Japan. A multicentric, double-blind comparison of 125 mg/day for 24 weeks vs. 250 mg/day for 24 weeks indicated that both groups experienced an equivalent amelioration rate of finger nail and toe nail onychomycosis (negative mycology test with KOH examination 83.3% vs. 88.6%) [13]. Therefore, treatment with 125 mg/day is currently widely accepted in Japan. The smaller size of patient body or race may be a factor augmenting the effect of the low dose, but these results from Japan may promote a budget program for treatment of onychomycosis through a low dose of terbinafine, especially for Asians. The standard dose of griseofulvin at 500–750 mg/day is used in Japan.

### 2.2.1.2 Candidiasis

#### 2.2.1.2.1 Etiology and Pathophysiology

The main causative agent is *C. albicans*, a common inhabitant of the gastrointestinal and genital tracts. Impairment of local barrier function of the skin by moisture, maceration, or friction permits the organism to thrive. If the immunological resistance of the host is impaired, candidiasis, may arise as an opportunistic infection.

#### 2.2.1.2.2 Clinical Features and Diagnosis

The basic clinical features on the skin are the presence of clearly demarcated scaly erythema with fine pustules and satellite papular or pustular lesions on intertrigenous areas (Fig. 2.2.2). On the mucous membrane,

---

**Take Home Messages**

> Detection of the pathogen from the lesion through mycological tests is essentially important.
> Superficial infections are usually successfully treated with topical antimycotics. Onychomycoses, hair infections, hyperkeratotic type of tinea pedis and manuum, certain types of tinea corporis, such as those indicating widely spread lesions, and follicular lesions or supplicative lesions require oral antimycotics.
a white membraneous material adheres, and red, sometimes erosive, patches appear after the removal of the white material. Diagnosis is made by the detection of yeast-like fungal elements and pseudo-hyphae under direct KOH examination. It can sometimes be isolated from normal oral cavity and skin by fungal culture.

2.2.1.2.3 **General Therapeutic Outlines**

Topical application of azoles, ciclopirox olamine, amorolfine, and terbinafine cream, once or twice a day for 1 or 2 weeks, has been proved a successful treatment option. For oral candidiasis in adults, treatments include oral antifungals such as miconazole gel, amphotericin B suspension 300 mg/day, or oral solution of itraconazole at 200 mg/day for 1 week. For vulvovaginal infections and sexual partners of candidial balanitis patients, topical use of antymycotic vaginal pessaries of azoles, such as clotrimazole or tioconazole, are useful.

True onychomycosis, caused by *Candida* sp., and secondary changes in the nails due to paronychia are distinguishable clinical entities [5]. In true onychomycosis (nail candidiasis), itraconazole 100–200 mg/day for 3–4 months is needed. Combination treatment of itraconazole 200 mg/day for 1 week for each month for 3 months and topical antymycotics is also recommended. Oral terbinafine is less useful. The secondary changes caused by paronychia can be treated with topical antymycotics.

2.2.1.2.4 **Current Established Therapies**

Oral use of itraconazole solution at 200 mg/day (up to 2 weeks) is effective for oro-esophagial candidiasis.

2.2.1.2.5 **Complications to Avoid**

A gradual increase in minimal inhibitory concentration (MIC) of oral fluconazole and itraconazole for *C. albicans* has been known. *Candida glabrata*, usually requiring higher MIC of azoles and terbinafine, may lead to refractory candidial vaginitis.

2.2.1.2.6 **Global Variation**

Fluconazole is yet to be officially approved for superficial candidiasis treatment in Japan; the efficacy of fluconazole 200 mg single use for oral candidosis on nonAIDS patients is known [14].

2.2.1.3 **Tinea Versicolor**

2.2.1.3.1 **Etiology and Pathophysiology**

Tinea versicolor is manifested as a chronic infection of the stratum corneum by *Malassezia* species, especially *M. globosa*.

2.2.1.3.2 **Clinical Features and Diagnosis**

Tinea versicolor appears as hyper or hypopigmented macules on the seborrhic regions on the trunk of young adults (Fig. 2.2.3). Eruptions are more common in hot and humid months. Itching is minimal. The diagnosis is made by the detection of fungal elements in scales on discolored skin lesions. Scotch tape is a feasible tool for stripping off scale from lesions. Short and thick fungal hyphae and large numbers of spore-like globular cells, referred to as “spaghetti and meatballs,” are characteristically observed upon direct KOH examination.

2.2.1.3.3 **General Therapeutic Outlines**

Topical application of azoles and terbinafine, once or twice a day for 1 or 2 weeks, has proved to be a successful treatment option. Patients with widespread

---

**Take Home Message**

- It is very important for the diagnosis of candidiasis to be confirmed by mycological tests, since some antymycotics such as benzylamine are less effective for the *Candida* species.
2.2 Fungal Infection

2.2.1.3.5 Complications to Avoid

Patients with a long history of tinea versicolor may retain discoloration of skin for a long time following successful treatment.

**Take Home Message**

- Scale from active lesions can easily be transcribed onto scotch tape by stripping. This finding is useful for diagnosis, determination of the lesion, evaluation of the treatment, and relapse.

2.2.1.3.6 Global Variation

A half dose of itraconazole (100 mg/day for a week) has been successfully used in Japan.

2.2.2 Subcutaneous Fungal Infection

**Key Features**

- Primary inoculum is introduced into the skin through puncture wounds, abrasions, or other trauma.
- Cutaneous lesions may be a manifestation of systemic dissemination of the fungi from visceral lesion.
- Fungal elements grow in the dermis and subcutis.
- Detection of the pathogen from a lesion by mycological and histopathological tests is essentially important.
- Dermal and subcutaneous fungal infections require oral antimycotics.

2.2.2.1 Sporotrichosis

2.2.2.1.1 Etiology and Pathophysiology

Sporotrichosis is a chronic granulomatous infection caused by *Sporothrix schenckii*, which is usually...
contracted via a minor penetration injury such as from a thorn or friction while working outdoors.

### 2.2.2.1.2 Clinical Features and Diagnosis

Initially, the lesion may be a red, painless small nodule with or without erosion (fixed type). Subsequently, patients may develop nodular lesions through regional lymphatic drainage (lymphocutaneous type). Diagnosis is confirmed by cultures from discharge, crusts around the ulcer, biopsy specimens, or typical histopathology and positive sporotrichin skin tests. Two or three weeks incubation on Sabouraud glucose agar at 27°C shows development of brownish gray molds on the slant. Higher temperature, such as 37°C, inhibits growth of the mycelium, and fungal growth is usually inhibited completely above 39°C. Histopathology indicates infectious granuloma with Langhans giant cell in the dermis and subcutaneous tissue. High-power view of PAS staining section shows spore-like fungal elements in suppurative microabscess or Langhans giant cell. Some fungal elements may be seen as asteroid bodies, and can sometimes even be distinguishable with HE staining. Sporotrichin skin test using purified antigen extracted from the culture media is usually positive, whereas other lymphangitic infections never show up as positive.

### 2.2.2.1.3 General Therapeutic Outlines

The most effective treatment is oral administration of potassium iodide (KI) in doses of 1 g/day for 2 months [15] to 6 g/day [16]. It is best to begin with 0.3–0.5 g/day, and then gradually increase if gastrointestinal adverse reaction is not evident. The species is susceptible to high temperature, so topical hyperthermia using a hot pack or heating pad, not exceeding 45°C, for 0.5–4 h/day for 2–4 weeks is a useful adjutant.

### 2.2.2.1.4 Current Established Therapies

Patients receiving either itraconazole at 100–200 mg/day for several months or terbinafine at 125–500 mg/day for an average of 10–12 weeks were cured of their infections, but the effects were no better than those of KI therapy. Moreover, cases of recurrence were reported among the patients treated with these newly developed antimycotics.

### 2.2.2.1.5 Complications to Avoid

Gastrointestinal trouble and thyroid dysfunction are likely during KI therapy [16]. Drug interaction with azoles and other drugs metabolized by the P450 system must be considered.

### Take Home Message

Two of three findings, that is, positive culture for *S. schenckii*, positive study for sporotrichin skin test, and histopathological findings consistent with sporotrichosis, are sufficient for clinical diagnosis and starting therapy for sporotrichosis with KI and local hyperthermia.

### 2.2.2.1.6 Global Variation

Doses of KI for treatment of sporotrichosis in western countries starts at 0.5–1.5 g/day and gradually increases to 4–6 g/day [16], whereas 1 g daily for 2–3 months is sufficient for most Japanese cases.

### 2.2.2.2 Dematiaceous (Brown-Pigmented) Fungal Infections

#### 2.2.2.2.1 Etiology and Pathophysiology

The infections are caused by dematiaceous fungi, a large heterogeneous group of molds with a pigmented hyphae containing melanin. The important cutaneous pathogens are *Alternaria* sp., *Exophiala* sp., *Fonsecaea pedrosoi* (*F. Monophora*), and *Phialophora* sp.. Infection is thought to follow traumatic inoculation. The CNS may become involved as a consequence of spread from skin lesions.

#### 2.2.2.2.2 Clinical Features and Diagnosis

The most prevalent clinical form is chromoblastomycosis caused by *F. pedrosoi, F. Monophora* a chronic
2.2 Fungal Infection

2.2.2 Verrucous plaque starting as a small pink scaly papule. Cystic lesions of phaeohyphomycosis caused by *E. jeaneselmei*, which is the next most common type, appear as an indolent subcutaneous abscess. Fungal cultures from lesions produce pigmented molds. Histopathological examinations exhibit round, thick cell-walled brown cells, termed muriform cells, in the lesions of chromoblastomycosis, or septate, mycelial elements in the lesions of phaeohyphomycosis. The fungal elements can be observed even on HE staining sections.

2.2.2.2 General Therapeutic Outlines

Smaller lesions are best treated by surgical excision. Larger lesions or eumycotic mycetoma are treated by a combination of surgery and antifungal therapy. Oral flucytosine, fluconazole, itraconazole, and terbinafine are used. Occasionally, intravenous amphotericin B may also be used [17]. Both cryosurgery and local hyperthermia [18] may be useful.

2.2.2.3 Current Established Therapies

Itraconazole (200–400 mg/day for up to 30 months) is currently the most effective agent for chromoblastomycosis. Terbinafine (500 mg/day for 12 months) is also reported to be effective for chromoblastomycosis caused by *F. pedrosoi*. Successfully treated cases with combination therapy or alternative week therapy with itraconazole and terbinafine have been reported [19].

2.2.2.4 Complications to Avoid

Incomplete excision causes recurrence and local dissemination of the lesion. Drug interaction with azoles and other drugs metabolized by the P450 system must be considered.

2.2.2.5 Take Home Message

- Smaller lesions are successfully treated by surgical intervention but extensive lesions are difficult to cure.
Infectious Diseases Society of America [22], secondary cutaneous cryptococcosis accompanied with CNS involvement is treated with amphotericin B, followed by fluconazole “consolidation” therapy. This chronic suppressive therapy with fluconazole is probably needed to prevent relapse.

### 2.2.2.3.4 Current Established Therapies

Voriconazole and liposomal amphotericin B are the main candidate antifungal treatments.

### 2.2.2.3.5 Complications to Avoid

Recurrence may occur with low (less than 200 mg/day) doses of fluconazole. Reduced dose of fluconazole is needed for patients with renal dysfunction. Drug interaction with azoles and other drugs metabolized by the P450 system must be considered.

---

**Take Home Message**

- Direct examination of discharge with Indian ink yields the most prompt diagnosis. Careful assessment for any CNS involvement is required.

---

**References**

11. Evans EG (1994) A comparison of terbinafine(Lamisil) 1% cream given for one week with clotrimazole(Canesten)1% cream given for four weeks in treatment of tinea pedis. Br J Dermatol 130(suppl 43):12–14
2.3.1 Herpes Simplex

2.3.1.1 Etiology and Pathophysiology

HSV is a double-stranded DNA virus transmitted through viral inoculation of susceptible mucous membranes or small breaks in the skin. The strains, HSV-1 and HSV-2, have two phases of infection. In the primary phase, the virus establishes itself in a nerve ganglion while the secondary, or recurrent, phase involves reactivation and replication of the virus under various systemic stimuli such as fever, sunlight, menses, stress, or breaks in the skin. Latent infection involves viral invasion of peripheral nerves and establishment of the virus in a dorsal root ganglion, most commonly the trigeminal ganglia in HSV-1 and the sacral nerve root ganglia in HSV-2. HSV-1 is most commonly associated with oral lesions and is transmitted through infected saliva. HSV-2 usually causes genital lesions and is transmitted sexually or during the passage of a newborn through the birth canal of an infected mother.

2.3.1.2 Clinical Characteristics and Diagnosis

The most frequently occurring manifestations of primary HSV-1 infection are pharyngitis, gingivostomatitis, and herpes labialis (cold sores). Characteristic lesions involve grouped vesicles on an erythematous base, which subsequently ulcerate or crust over, and last for 2–6 weeks. Patients may complain of headache, malaise, tenderness, paresthesias, pain, or burning before the eruption of vesicles in a particular area. Vesicles develop and rupture within 2–4 days and resolve after approximately 8 days. Associated systemic symptoms such as fever, malaise, and tender lymphadenopathy are rare in recurrent infection and, if present, may be signs of secondary infection. HSV-2 is most commonly associated with recurrent infections in the genital area. Severity and rate of recurrence vary from patient to patient.
Diagnosis is made clinically and can be confirmed through viral culture by obtaining a swab from the base of a vesicle. A Tzanck smear demonstrating the presence of multinucleated giant cells can also confirm a diagnosis, although this method does not distinguish between HSV-1, HSV-2, and varicella-zoster virus (VZV). Newer molecular assays involving the use of PCR can be used for the rapid detection of HSV DNA. Immunofluorescent tissue staining and antibody testing are available in some laboratories [1].

2.3.1.3 Current Established Therapies

Oral antiviral agents (Table 2.3.1.) can be started at the first sign or symptom of infection and are most effective when taken within 48 h. Suppressive therapy is aimed at reducing recurrence or preventing transmission to a partner during an active infection. Topical antiviral agents, such as tetracaine I. Eight percent cream (Cepacol Viractin Cream) and penciclovir cream (Denavir) can be applied to promote healing and reduce the duration of lesions by 12–48 h. Docosanol 1% cream (Abreva) is used for herpes labialis [2–12].

2.3.1.4 Experimental Approaches

Experimental therapies used to treat HSV infections include immunomodulatory agents, such as imiquimod and resiquimod. These agents induce an antiviral immune response through the activation of cytokines, particularly tumor necrosis factor-alpha, interferon-alpha and gamma, and interleukin-12 [13]. A promising, investigational vaccine protective against genital herpes is currently in phase II clinical research trials across the US.

Table 2.3.1 Antiviral therapy for HSV-1 and HSV-2 infections

<table>
<thead>
<tr>
<th>Drug name</th>
<th>First episode of mucocutaneous infection</th>
<th>Herpes labialis</th>
<th>Recurrent genital herpes</th>
<th>Chronic suppressive therapy</th>
<th>Infection in immunocompromised hosts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valacyclovir (Valtrex)</td>
<td>I g twice a day for 10 days</td>
<td>2 g twice a day for 1 day</td>
<td>500 mg twice a day for 3 days</td>
<td>500 mg/day or 1 g/day</td>
<td>500 mg–1 g a day</td>
</tr>
<tr>
<td>Acyclovir (Zovirax)</td>
<td>200 mg 5 times a day for 10 days</td>
<td>400 mg 3 times a day for 5 days</td>
<td>200 mg 5 times a day for 5 days or 400 mg 3 times a day for 5 days</td>
<td>400 mg 2–3 times a day</td>
<td>5–10 mg/kg IV 3 times a day for 5–10 days for severe infection</td>
</tr>
<tr>
<td>Famciclovir (Famvir)</td>
<td>250 mg 3 times a day for 7–10 days</td>
<td>1,500 mg (one dose)</td>
<td>125 mg 2 times a day for 5 days or 1,000 mg 2 times a day for 1 day</td>
<td>250 mg twice a day</td>
<td>500 mg twice a day for 7 days</td>
</tr>
</tbody>
</table>

Take Home Message

 HSV infection is very common and typically presents with prodromal symptoms. The impact of HSV infection can be significant due to frequent recurrences. Current established therapies are relatively effective at treating these recurrences. Experimental agents are being developed to aid in the treatment and prevention of HSV infection.

2.3.2 Varicella and Zoster

2.3.2.1 Etiology and Pathophysiology

Varicella, commonly known as chickenpox, is caused by the VZV. This highly contagious virus colonizes the upper respiratory tract via transmission through airborne droplets or contact with vesicular fluid. Viral incubation is from 10 to 21 days. A prodromal phase, lasting 7–14 days, consists of low-grade fever, abdominal pain, headache, pruritus, malaise, anorexia, cough, coryza, sore throat, and is followed by a vesicular rash. The infectious period begins 2 days before the eruption of skin lesions and lasts approximately 5–6 days after the crusting of all lesions.
### 2.3.2.2 Clinical Characteristics and Diagnosis

The characteristic rash initially appears as red macules, which then progress to papules (Fig. 2.3.1), vesicles, pustules, and crusts. New lesions appear for 3–5 days. The typical description of “dew drops on a rose petal” is attributed to vesicles on an erythematous base. The hallmark of the varicella rash is the simultaneous presence of skin lesions at different stages. The extent of lesions and degree of pruritus varies from patient to patient. Pustules crust over after 6–7 days, and lesions tend to heal without scarring. Swelling, extensive erythema, fever lasting for more than 4 days, prolonged eruption of new lesions, or delayed healing may be signs of bacterial superinfection or impaired cellular immunity.

Herpes zoster, or shingles, results from viral reactivation months to years after primary infection and typically affects a single dermatome region. The incidence of zoster increases with age and is more common in immunocompromised hosts. Patients may complain of constitutional symptoms and burning, pain, or itching in a localized area before the eruption of vesicles. The most common location of zoster is the thoracic region. Ocular complications from ophthalmic zoster can result from viral infection involving a branch of the ophthalmic nerve. Another debilitating sequela of zoster is postherpetic neuralgia (PHN), which is persistent pain for months or years in a dermatome area.

Diagnosis is made based on clinical findings, making laboratory studies unnecessary in most cases. A viral culture and Tzanck smear can confirm a diagnosis. Different serology tests are available, yet are more commonly used only to confirm prior infection [14, 15].

### 2.3.2.3 Current Established Therapies

Therapy consists of symptomatic relief with antipruritic lotions and antihistamines in uncomplicated cases. Acyclovir may decrease symptoms and promote faster healing. Acyclovir is most beneficial in adolescents, adults, and immunocompromised hosts. Antipyretics can be used to reduce fever, although aspirin should be avoided in children due to its association with Reye’s syndrome. Varicella zoster immune globulin (VZIG) should be given to susceptible (that is, seronegative) neonates, adolescents, adults, pregnant women, and immunocompromised hosts within 96 h of exposure to reduce complications and decrease mortality. The varicella vaccine should be administered to healthy children starting at 1 year of age, as well as to seronegative adolescents and adults. Individuals with a reliable history of previous infection do not need vaccination since recurrent varicella is very rare.

For cases of zoster, wet compresses may provide symptomatic relief. In addition to analgesics, other concomitant therapies may include systemic steroids, ganglion or epidural nerve blocks with bupivacaine 0.25%, oral gabapentin, or pregabalin. Acyclovir, valacyclovir, and famciclovir may promote a shorter course of infection and faster healing as well as decrease severity and duration of PHN (Table 2.3.2). A live attenuated VZV vaccine called Zostavax has recently been approved by the FDA to prevent shingles in patients aged 60 years and above. In a randomized, double-blind, placebo-controlled study, the vaccine decreased incidence and morbidity from disease as well as reduced the incidence of PHN [16–23].

#### Table 2.3.2 Therapy for VZV infection

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Adults:</th>
<th>Children:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>800 mg, 5 times a day for 7 days</td>
<td>80 mg/kg/day divided in 4–5 doses for 5 days (not to exceed 3,200 mg/day)</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>1 g, 3 times a day for 7 days</td>
<td></td>
</tr>
<tr>
<td>Famciclovir</td>
<td>500 mg, 3 times a day for 7 days</td>
<td></td>
</tr>
</tbody>
</table>

*aSame dose in children with encephalitis or pneumonia*
2.3.3 Human Papillomavirus

2.3.3.1 Etiology and Pathophysiology

There exist more than 100 different strains of human papillomavirus (HPV). Infections are highly contagious, and viral incubation is from 1 to 6 months. “Low-risk” types, such as HPV-2 cause verruca vulgaris (common warts) and 6 and 11 cause condyloma acuminatum (genital warts). Transmission is through direct contact with lesions. Cancerous lesions of the skin of the penis, vulva, and inner linings of the vagina, cervix, and rectum have been associated with types 16 and 18. Fiat and plantar warts are other benign variations caused by HPV-3 and HPV-1, respectively.

2.3.3.2 Clinical Characteristics and Diagnosis

Common warts are hyperkeratotic, epidermal proliferations occurring most commonly on the hands, periangual skin, elbows, knees, and plantar surfaces. Fiat warts are flat-topped papules typically found on the forehead, dorsal surface of the hands, chin, neck, and legs. Cauliflower-like lesions on the perianal area, vagina, labia, and vulva are characteristic of condyloma acuminatum.

Diagnosis is usually made based on clinical findings, although a tissue biopsy can confirm a diagnosis. A Pap smear serves as a screening test for cervical dysplasia. Abnormal Pap smear results may warrant further testing with 3–5% acetic acid and colposcopy along with HPV DNA typing.

2.3.3.3 Current Established Therapies

Due to high rates of recurrence, multiple treatments for warts are usually required over a course of weeks to months. However, spontaneous resolution may occur with time. Treatment for warts is usually topical, most commonly with salicylic acid preparations and liquid nitrogen cryotherapy. Immunomodulatory agents such as imiquimod and interferon alpha can be used for external anogenital warts and condyloma acuminatum. Intraleisonal bleomycin (0.5 U/mL) or surgical treatment with electrodesiccation and curettage may be indicated for resistant or severe cases. Immunocompromised patients may require more aggressive therapy (combination treatment) due to a higher incidence of extensive disease and greater resistance to therapy. Although expensive, laser therapy is another treatment option. A gynecologic oncologist should be consulted for management of cervical neoplasia.

FDA and EMEA recently approved a quadrivalent vaccine against HPV types 6, 11, 16, and 18. The vaccine targets the most common subtypes associated with condyloma acuminatum (6 and 11) and cervical cancer (16 and 18) and is approved for females aged 9–26. It is given in three injections over a 6-month time period [23–29]. A bivalent vaccine against HPV types 16 and 18 is licensed in Australia and the EU.

Take Home Message

- VZV is responsible for both chickenpox and shingles, a latent reactivation of the virus. Treatment is primarily directed at providing symptom-directed relief, although antivirals may shorten the course. Vaccines exist for the prevention of both chickenpox and shingles.

- HPV infection is very common and a leading cause of cervical cancer in females. Vaccines are available and highly recommended.
2.3.4.2 Clinical Characteristics and Diagnosis

Characteristic skin lesions consist of shiny, white to flesh-colored, firm, umbilicated papules (Fig. 2.3.2). In children, lesions occur most commonly in the face, upper trunk, and extremities. Papules around the eyes usually result from autoinoculation. Lesions on the lower abdomen, genitalia, and upper thighs are most common in young adults and result from sexual transmission of the virus. Patients with eczema are more prone to developing lesions in areas of inflamed skin. Immunocompromised patients tend to have more aggressive disease with an increased number of larger skin lesions. Most lesions are not painful or itchy and tend to resolve without treatment within 6–9 months, although papules may persist for as long as 24 months. Signs of inflammation around a papule may signify involution and subsequent resolution.

Diagnosis is made based on clinical findings. A skin biopsy showing intracytoplasmic viral inclusions may confirm a suspected diagnosis. A biopsy is recommended in immunocompromised hosts in order to rule out other skin conditions, such as cryptococcosis and histoplasmosis, which may mimic MC in these patients.

2.3.4.3 Current Established Therapies

Treatment options vary depending on individual cases. Due to spontaneous resolution, no therapy may be indicated in immunocompetent patients. In order to decrease transmission and autoinoculation, patients should be advised to avoid direct skin-to-skin contact and avoid shaving around lesions. Curettage, cryosurgery, and adhesive surgical tape changed daily are effective treatment options and rarely result in scarring. Other topical treatment options include tretinoin, cantharidin 0.7% solution with occlusion, imiquimod, and 10% KOH, which may cause skin irritation or scarring. Less commonly used therapies include topical cidofovir (a nucleoside analog) and pulsed dye laser [30–33].

Take Home Message

→ MC is a common disease in children. When observed in adults, co-infection with HTV must be ruled out.

2.3.5 Hand, Foot, and Mouth Disease

2.3.5.1 Etiology and Pathophysiology

Hand, foot, and mouth disease (HFMD) is a highly contagious viral infection causing a characteristic vesicular eruption involving the oral cavity, hands, and feet. Epidemics of HFMD are most commonly caused by coxsackievirus A16 and enterovirus 71, although other serotypes cause sporadic cases. Viral transmission occurs by direct contact with nasal or oral secretions, fecal material, or aerosolized droplets. Viral
incubation is from 3 to 6 days, with a 1–2 day prodromal syndrome consisting of sore throat, malaise, low-grade fever, abdominal pain, anorexia, and cough. The virus tends to spread to the lymph nodes within 24 h of inoculation, and patients may be affected by submandibular and/or cervical lymphadenopathy.

### 2.3.5.2 Clinical Characteristics and Diagnosis

Characteristic features include painful, aphthae-like erosions, present for 5–10 days, found anywhere in the oral cavity. The palate, buccal mucosa, gingival, and tongue may all be involved. Two-thirds of patients will manifest cutaneous lesions involving the hands, feet, and buttocks 24 h after the eruption of oral lesions. Cutaneous lesions heal without scarring in about 7 days. Initially, lesions appear as erythematous macules that progress to pale, gray, elliptical vesicles. The face and legs are less commonly involved. The number and distribution of vesicles vary from patient to patient.

Diagnosis is made based on clinical findings. A viral culture obtained from the swabs of the vesicles, throat, or stool can confirm a diagnosis. High titers of complement-fixing antibodies may be present in the convalescent phase. New, molecular assays using PCR can be used to rapidly distinguish between coxsackievirus A16 and enterovirus 71 in cases of outbreaks or epidemics.

### 2.3.5.3 Current Established Therapies

HFMD is usually mild and self-limiting. Treatment is targeted at symptomatic relief with topical anesthetics, such as viscous lidocaine, dyclonine solution, or diphenhydramine. Acetaminophen can be used to control fever and pain. Antacid agents, such as sulcrate and magnesium hydroxide, may promote ulcer healing. Patients should be monitored for dehydration [34–38].

### 2.3.5.4 Complications to Avoid

Viral infections can cause significant morbidity and mortality, particularly in immunocompromised hosts. Bacterial and fungal superinfections may complicate an existing infection. Ocular infections caused by HSV can result in significant corneal scarring and blindness if untreated. HSV encephalitis may cause permanent neurologic damage even with appropriate treatment and is associated with a 70% mortality rate if untreated. Disseminated HSV infection can result in esophagitis, adrenal necrosis, interstitial pneumonitis, cystitis, arthritis, meningitis, encephalitis, fulminant hepatitis, leukopenia, thrombocytopenia, and disseminated intravascular coagulation [1, 35].

### References

2.3 Viral Infections

Nearly one million new people are infected with a sexually transmitted infection every day worldwide.

### 2.4 Syphilis

#### 2.4.1 Epidemiology and Pathophysiology

Syphilis is a sexually transmitted disease caused by the spirochaete *Treponema pallidum*. In the USA, 7,980 cases of syphilis were registered in 2004. Eighty-five percent were men. Especially the number of cases in men who have sex with men is rising in the last years. The incidence is 2.7 per 100,000 inhabitants [1].

**2.4.1.2 Clinical Characteristics and Diagnosis**

After 3 weeks an ulceration (90% genitoanal localization) occurs at the place of infection together with regional lymphadenopathy. After 9–12 weeks the secondary stage presents with bacteremia, general symptoms, and a great variety of skin manifestations. Without treatment, tertiary syphilis with granuloma (gumma) can develop after a latency phase of years [2] (Table 2.4.1). Cardiovascular and neurosyphilis can also be complications of untreated *Treponema pallidum* infection. In patients with HIV infection, these stages can be seen earlier.

Histologically a plasmacellular infiltrate is characteristic. Dark field microscopy of the secretion of primary ulceration is an easy diagnostic method. For differentiation of apathogenic treponema a FITC marked antibody can be used. A PCR is possible but specificity and sensitivity are not yet optimal.

For screening *Treponema pallidum*, hemagglutination test (TPHA) or *Treponema pallidum* particle agglutination test (TPPA) is used. They are positive after 2–3 weeks and stay positive even after adequate therapy. Cardiolipin and veneral disease research laboratory (VDRL) can be used to determine the need for treatment. These tests are positive after 4–6 weeks but not specific for *Treponema pallidum*. False positive results can be seen in patients with other infections, autoimmune disease, and malignancies [3].
To confirm the infection, the fluorescence treponema antibody absorption test (FTA-abs) is most specific. Cross-reactivity with *Borrelia burgdorferi* can sometimes be seen. The 19 S-IgM–FTA abs test can be used to monitor treatment and should be negative after adequate treatment. Lipoid antibodies should be controlled every 3 months within the first year after treatment. For baseline antibody levels 2–4 weeks after treatment should be used. One year after effective therapy, lipoid antibodies should be 3–4 titer steps lower than baseline. TPHA/TPPA should be constant or decreasing. Rising titers can be seen in insufficient treatment or reinfection. A differentiation between reinfection and reactivation with antibody tests is not possible [4, 5].

For the diagnosis of connatal syphilis, serum probes of the mother and the child should be compared. IgM antibodies that are higher than the mothers’ or persisting antibodies within the first year are characteristic for connatal syphilis [6].

### 2.4.1.3 Therapeutic Outline

Penicillin is still the first-line therapy [7]. Because of the slow replication cycles of *Treponema pallidum* a minimum treatment of 10 days is needed. A serum level of >0.018 μg/mL is needed for penicillin G to reach treponemocid levels. With intramuscular treatment these levels cannot be achieved in the central nervous system [8, 9]. If neurosyphilis is suspected intravenous treatment is mandatory [10]. Two to eight hours after the beginning of treatment fever, headache and other symptoms can occur (Jarisch-Herxheimer reaction). It can be treated or better prevented with 0.5–1 mg predisolone/kg bw p.o.

### 2.4.1.4 Current Established Therapy

Single shot treatment with benzathine penicillin is recommended for early syphilis (up to 1 year after infection).

In cases of penicillin allergy, doxycyclin 2 × 100 mg for 14 days or erythromycin or tetracyclin 4 × 500mg for 14 days or Ceftriaxon 1 g/day for 10 days can be used. Macrolides (e.g., azithromycin) should be avoided because resistance has been described [11].

In late syphilis (after 1 year postinfection or unknown time of infection) neurosyphilis and mesarthritis syphilitica should be excluded before treatment. Benzathine penicillin 2.4 Mio i.E. i.m. day 1, 8, and 15 is recommended. For neurosyphilis penicillin G i.v. 20–30 Mio i.E./day in 3–6 doses for 14–21 days is first-line therapy. Ceftriaxone 2 g i.v. for 14 days has proved to be effective although some cases of treatment failure have been seen especially in HIV positive patients [12, 13]. Doxycycline 4 × 200 mg for 28 days should only be used in neurosyphilis if no other options (premedication with steroids prednisolone 1 mg/kgbw i.v., desensibilisation) are available [14] (Table 2.4.2). Partner notification and treatment is important to minimize the risk of reinfection.

### 2.4.1.5 Complications

About 15% of patients with syphilis are HIV positive and up to 80% of HIV-infected patients have syphilis antibodies. Hence HIV positive patients should be screened for syphilis every 6–12 months and every patient with syphilis should be screened for other STDs [15]. All HIV positive patients should be offered a cerebrospinal fluid puncture because neurosyphilis is more common and different stages can occur shortly after the infection [9, 16].

### 2.4.1.6 Global Variations

Migration and reduced condom use still lead to a rising incidence of STDs. Treatment has to be adapted to topical resistance. STD and HIV prevention programs have to be consistently promoted.
### 2.4 Sexually Transmitted Diseases (STDs)

#### 2.4.2 Gonorrhea

**2.4.2.1 Epidemiology and Pathophysiology**

Worldwide 300–600 million infections with *N. gonorrhoeae* are estimated. In 2001, 361,705 cases were reported in the US (600,000 new infections are estimated) [4]. *N. gonorrhoeae* are gram-negative diplococci that can be detected within polymorphonuclear leukocytes. *N. gonorrhoeae* is sexually transmitted and can also be acquired at birth.

**2.4.2.2 Clinical Characteristics and Diagnosis**

*N. gonorrhoeae* causes symptomatic urethritis and occasionally epididymitis in men. Rectal and pharyngeal infections are often asymptomatic (92%, [17]). Gonorrhea is also often asymptomatic among females (45%, [18]) but can cause serious complications like pelvic inflammatory disease, tubal infertility, and ectopic pregnancy if untreated.

Neonatal infection can cause severe conjunctivitis resulting in blindness if not treated and rarely sepsis with meningitis, endocarditis, and arthritis.

Nucleic acid amplifications tests (NAATs) for *N. gonorrhoeae* show good sensitivity and specificity. They have been developed and approved for endocervical or urethral swabs. Urine tests are less sensitive. NAATs are not recommended for rectal or oropharyngeal specimens. For nongenital tract specimens *N. gonorrhoeae* culture is still considered to be the gold standard. Although the detection rate is lower, it can differentiate apathogenic diplococci and resistance testing can be performed. Point of care testing is less sensitive but can be considered if immediate treatment is necessary (e.g., because of missing compliance) [19].

**2.4.2.3 Therapy**

Single shot treatment with spectinomycin 2 g i.m. or ceftriaxon 0.25 g i.v. is preferred. A growing resistance against chinolones and azithromycin can be seen. Treatment guidelines have to be reassessed on a regular basis considering topical resistance profile [20]. Partner notification and treatment is important to minimize the risk of reinfection.

**2.4.2.4 Complications**

Up to 20–40% of patients with gonorrhea are coinfectected with *Chlamydia trachomatis*. A screening for other STDs should be performed. Rarely topical infection disseminates with arthritis, meningitis, or endocarditis. Autoimmune reactions like Reiter’s disease can also be seen.

### 2.4.3 Trachomatis

**2.4.3.1 Epidemiology and Pathophysiology**

An infection with *Chlamydia trachomatis* is the most frequently reported sexually transmitted disease in most countries. About three million infections occur annually in the United States [19].

<table>
<thead>
<tr>
<th>Table 2.4.2 Therapy of syphilis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
</tr>
<tr>
<td>Early syphilis with primary-infection or up to 1 year after infection</td>
</tr>
<tr>
<td>Late syphilis without neurosyphilis or cardiovascular syphilis and HIV-infected patients</td>
</tr>
<tr>
<td>Neurosyphilis und cardiovascular syphilis</td>
</tr>
</tbody>
</table>
2.4.3.2 Clinical Characteristics and Diagnosis

*Chlamydia trachomatis* causes symptomatic urethritis and occasionally epididymitis in men. Rectal and pharyngeal infections are often not symptomatic (86%). It is also often asymptomatic among females (>50%) but can cause serious complications like pelvic inflammatory disease, tubal infertility, and ectopic pregnancy if untreated [4].

NAATs for *Chlamydia trachomatis* show good sensitivity and specificity. They have been developed and approved for endocervical or urethral swabs, but can also be used for urine samples. NAATs are not recommended for rectal and oropharyngeal specimens. For nongenital tract specimens chlamydia culture is still considered to be the gold standard. Although the detection rate is lower, it can differentiate apathogenic specimen and resistance testing can be performed. It should also be used for legal investigations. Point of care testing is less sensitive but can be considered if immediate treatment is necessary (e.g., because of missing compliance or in resource poor areas) [15, 21]. Serum testing has limited value because it cannot distinguish between previous chlamydial infection and active disease.

2.4.3.3 Therapy

A recent meta-analysis of 12 randomized clinical trials of azithromycin vs. doxycycline for the treatment of chlamydia infection demonstrated equal efficacy with cure rates of 97% and 98% [4, 22]. Partner notification and treatment is important to minimize the risk of reinfection.

<table>
<thead>
<tr>
<th>Recommended</th>
<th>Azithromycin</th>
<th>Single dose:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1,000 mg p.o.</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>2 × 100 mg p.o.</td>
<td>for 7 days</td>
</tr>
</tbody>
</table>

Alternative

<table>
<thead>
<tr>
<th>Erythromycin</th>
<th>4 × 500 mg p.o.</th>
<th>for 7 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ofloxacin</td>
<td>2 × 300 mg</td>
<td>for 7 days</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>1 × 500 mg</td>
<td>for 7 days</td>
</tr>
</tbody>
</table>

2.4.4 Lymphogranuloma Inguinalis

2.4.4.1 Etiology and Pathophysiology

Lymphogranuloma inguinalis (syn. Lymphogranuloma venereum) is a sexually transmitted infection with *Chlamydia trachomatis* serotype L1–L3. It is endemic in many tropical and subtropical regions. Lately an outbreak among men who have sex with men has been seen in Europe [23]. Men suffer 5–10 times more often from the disease, but many infections in women are not symptomatic.

2.4.4.2 Clinical Characteristics and Diagnosis

Lymphogranuloma inguinalis is seen in three stages:

**Stage I:** After 5–10 days a papule develops and forms an ulcer.

**Stage II:** After 2–4 weeks swelling (bubo) of inguinal lymph nodes and sometimes fistulation and perforation of abscesses, intraabdominal bubo in cases of vaginal or rectal primary lesion are seen.

**Stage III:** Elephantiasis genitoanorectalis ulcerosa is a complication after long-lasting infection without effective treatment.

Rectal infection might result in proctocolitis (including mucoid and/or hemorrhagic rectal discharge, anal pain, constipation, fever, and/or tenesmus) and might lead to chronic, colorectal fistulas and strictures [24, 25].

For diagnosis see chlamydia (Sect. 2.4.3). Only specialized laboratories can perform specific tests for serotype L1–3 [4].

2.4.4.3 Therapy

The therapy should be longer than that for other chlamydia infections. Most experts recommend 3 weeks [4]. Partner notification and treatment is important to minimize the risk of reinfection.
### 2.4 Sexually Transmitted Diseases (STDs)

#### 2.4.4 Sexually Transmitted Diseases (STDs)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>I and II</td>
<td>Doxycycline 2×100 mg for 3 weeks or Cotrimoxazole 2×960 mg for 14 days or Ofloxacin 2×300 mg for 7–14 days or Tetracycline or Erythromycin 4×500 mg for 14 days</td>
</tr>
<tr>
<td>III</td>
<td>Surgery + antibiotics</td>
</tr>
</tbody>
</table>

#### 2.4.4.4 Complications

Like in all chlamydia infections, tubal infertility and ectopic pregnancy can result.

#### 2.4.5 Chancroid (Ulcer molle)

##### 2.4.5.1 Epidemiology and Pathophysiology

Infection with *Haemophilus ducreyi* causes sexually transmitted genital ulcerative disease. It is most often seen in tropical and subtropical regions and European metropolis or harbors. About 7 million infections per year are estimated to be seen worldwide.

##### 2.4.5.2 Clinical Characteristics and Diagnosis

After 2–5 days, confluent papules form a painful ulcer in the genitonalan region together with regional lymphadenitis and sometimes lymph node abscesses or fistulas. Often autoinoculation can be seen. The diagnosis can be confirmed by culture and microscopy (gram-positive rods) but sensitivity is <80% even with special culture media [26]. Differential diagnosis includes syphilis, lymphogranuloma inguinale, and genital herpes.

##### 2.4.5.3 Therapy

Local therapy with antiseptic agents, e.g., polyvidon-iodine and drainage of abscesses should be combined with systemic antibiotics. Partner notification and treatment is important to minimize the risk of reinfec-

| First line | Azithromycin | Single dose: 1,000 mg p.o. |
| Alternative | Erythromycin | 3–4×500 mg/day p.o. for 7 days |
| Ceftriaxone | 0.25 g i.m. single dose |
| Ciprofloxacin | 2×500 mg/day p.o. for 3–5 days |

#### 2.4.5.4 Complications

Fistulation and destructive scarring can be seen if untreated. All patients should be screened for other sexually transmitted diseases. Autoimmune disease like erythema nodosum can be induced [28].

#### 2.4.6 Granuloma Inguinale (Donovanosis)

##### 2.4.6.1 Ethiology and Pathophysiology

Endemic sexually transmitted granulomatous infection in tropical and subtropical regions caused by *Calymmatobacterium granulomatis* (Donovania granulomatis). *Calymmatobacterium granulomatis* belongs to Klebsiella subspecies and is a gram-negative intracellular rod [29].

##### 2.4.6.2 Clinical Characteristics and Diagnosis

After 1–12 weeks painful or itching papula or noduli occur. Later they are confluent and ulceration with hypertrophic granulation can be seen. Women are often asymptomatic. Diagnosis with culture is difficult. With Giemsa staining Donovan bodies (mononuclear cells with intracellular bacteria) can be detected [30].
2.4.6.3 Complication

Without treatment secondary infection and lymphoedema can be a complication. Other sexually transmitted diseases should be ruled out.

2.4.6.4 Therapy

Topical therapy with antiseptic agents e.g., polyvidone-iodine and drainage of abscesses should be combined with systemic antibiotics. Treatment should be given for 2–4 weeks or until all skin lesions are healed. Partner notification and treatment is important to minimize the risk of reinfection.

<table>
<thead>
<tr>
<th>First line</th>
<th>Cotrimoxazol</th>
<th>4×500 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternative</td>
<td>Tetracycline</td>
<td>4×500 mg/day p.o.</td>
</tr>
<tr>
<td></td>
<td>Doxycycline</td>
<td>2×100 mg</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Azithromycine</td>
<td>1×1 g per week</td>
</tr>
<tr>
<td></td>
<td>Erythromycine</td>
<td>4×500 mg</td>
</tr>
</tbody>
</table>

2.4.7 Other Sexually Transmitted Diseases

- Trichomoniasis
- Genital Herpes
- Candida
- Condylomata acuminata
- Pediculosis
- Scabies
- Urethritis
- Viral hepatitis
- CMV

References

2.5 Etiology and Pathophysiology

In 1981, first reports of unusual opportunistic infection and Kaposi’s sarcoma rapidly leading to death in young homosexual men in San Francisco were published [1]. This was the beginning of the AIDS epidemic. HIV was described as causing the disease in 1983 by Barre-Sinoussi and Gallo [2, 3]. In 1986, HIV2 was described by Clavel [4]. HIV is a lymphotropic and neurotropic retrovirus belonging to the group of lenti-viruses.

In 2006 ca. 39 Mio million people were infected worldwide, 4.1 million people became newly infected, and 2.8 million people lost their lives to AIDS. Among these, 44.8% were female. Men who have sex with men, sex workers, i.v. drug users, and prisoners tend to have a higher rate of HIV infection in most countries, but percentages vary greatly, and infections by heterosexual contacts and mother to child transmission became increasingly important [5, 6].

The HI virus reproduces within the CD4 helper cells. It recognizes the CD4 receptor and docks on. With the help of co-receptors such as CCR5 and CXCR4, it can penetrate into the human cell. There is a diversity of CCR5 receptor polymorphisms that can influence the course of HIV infection. CCR5 receptor blocking agents have been developed and approved recently. Fusion inhibitors can block virus-derived glycoproteins, for example, gp 41 and gp 120. After penetration into the human cell, viral RNA is transcribed into DNA. Transcription is mediated by the reverse transcriptase that can be blocked by nucleoside reverse transcriptase inhibitors (NRTIs) by inserting nucleoside analogs. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) cause a change in the enzyme configuration. During the replication of the virus, regulator proteins (tat, nef, env) are switched on and off. This therapeutic target could not be used successfully so far. After RNA has been transcribed, the DNA is transported into the nucleus and integrated into the human genome. In this process, HIV-integrase is an important key enzyme. The first integrase inhibitor was approved in 2007. The assembly of an infectious virus particle is a multilevel process. The HIV protease cuts the viral gag-pol polyprotein into its functional domains.

Key Features

- Skin lesions can be the first sign of immunodeficiency.
- For diagnosis, an ELISA has to be confirmed by a western blot.
- With combination antiretroviral therapy, quality of life and life expectancy can be significantly increased.
- While Kaposi sarcoma is seen less frequently after the introduction of antiretroviral therapy, human papillomavirus (HPV) related cancer and other non-AIDS-defining cancers are increasingly challenging.
- Human immunodeficiency virus (HIV) patients should be treated in specialized centers because of possible side effects, resistance, and drug interactions associated with antiretroviral therapy.
subunits. If the protease is inhibited and proteolytic splicing prevented, non-infectious virus particles will result. The so-called maturation inhibitors inhibit HIV-replication in a very late phase of the HIV reproduction cycle, that is, by the budding or maturation of new virions (Fig. 2.5.1) [7].

2.5.2 Clinical Characteristics

If no treatment is initiated, different phases of the HIV infection can be seen. In the first few weeks, an acute HIV infection syndrome with flu-like symptoms and rashes can occur. It normally resolves after a maximum of 4 weeks. After this, most patients have no health problems for several years or mild symptoms such as lymphadenopathy. Later, HIV-related symptoms show a deterioration of the immune competence. The skin is a reflection of the immune system. HIV-positive patients often present with skin or mucosal problems (for example, herpes zoster, thrush) as a first sign of the infection [8]. AIDS is the last stage of the HIV-infection. AIDS-defining illnesses are listed in the CDC classification of HIV (Tables 2.5.1 and 2.5.2). Before the era of antiretroviral therapy, most patients died within 2 years of the first manifestation of AIDS-defining complications. Without therapy, up to 90% of all HIV-infected patients die from AIDS [9].

2.5.2.1 HIV and Pregnancy

In many countries, voluntary HIV-testing is part of prenatal care. With a combination of antiretroviral therapy and cesarean section, vertical transmission could be reduced to 1–2%. HIV-positive pregnant women should be cared for and treated according to international guidelines [10].

2.5.2.2 HIV and Tumors

In the beginning of the HIV epidemic, Kaposi’s sarcoma was a common stigma in AIDS patients and one of the leading causes of death. While Kaposi’s sarcoma is observed less frequently after the introduction of antiretroviral therapy, lymphoma and other malignancies are increasingly challenging. A survey in French clinics specialized in HIV showed that 28% of all HIV positive patients’ deaths were tumor-related. 45% of those were non-AIDS-defining tumors [11].

The incidence of HPV-related anal carcinoma and its precursor lesions is rising dramatically. Compared to the general population, concomitant HIV infection drastically increases the relative risk for anal intraepithelial neoplasia (AIN) and anal cancer (60.1 and 37.9, respectively). Perianal HPV infections have been detected in up to 93% of men who are HIV positive, and a high incidence of high-grade AIN has been reported. Screening programs, as they are already established for cervical carcinoma, should be implemented [12]. HIV-positive patients have an 8 times higher risk of developing lung cancer. They are younger, and the tumor (predominantly adenocarcinoma) grows rapidly. Smoking is an important risk factor. The risk of developing hepatocellular carcinoma is determined by hepatitis B and C coinfection. Chronic hepatitis is more common in HIV-positive patients and leads faster to cirrhosis. Early hepatitis treatment and prevention of hepatitis B by vaccination are important to reduce liver-associated deaths [11].

2.5.2.3 Diagnosis

The standard screening test for HIV is the ELISA. If positive, it has to be confirmed by a second test, for
2.5 Human Immunodeficiency Virus (HIV)

There is a diagnostic window of 3 months after the infection when the test can be false negative. Rapid HIV tests can be helpful in emergency rooms, developing countries, or after occupational HIV exposure. They should be confirmed by a standard test as soon as possible.

HIV antibodies can be found in newborns of HIV-positive mothers for up to 12–15 months. A perinatal infection has to be excluded by PCR.

After the confirmed first diagnosis of HIV infection, the patient should be referred to an HIV specialist. Other infections such as hepatitis, sexually transmitted diseases (STDs), tuberculosis, and toxoplasmosis should be ruled out. To determine whether a patient needs to be treated with antiretroviral therapy, the patient should be screened for opportunistic infection and other HIV-associated conditions. The CD4-cell count and viral load should be determined [13, 14].

### Table 2.5.1 Clinical categories of the CDC classification system in HIV-infected persons [9]

| Category A | Category C – AIDS-defining illnesses$^b$
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic HIV infection</td>
<td>Candidiasis of bronchi, trachea, or lungs</td>
</tr>
<tr>
<td>Acute (primary) HIV infection with accompanying illness or history of acute HIV infection</td>
<td>Candidiasis, esophageal</td>
</tr>
<tr>
<td>Persistent generalized lymphadenopathy</td>
<td>Cervical cancer, invasive$^a$</td>
</tr>
</tbody>
</table>

| Category B | Category C – AIDS-defining illnesses$^b$
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic conditions$^a$ that are not included among conditions listed in clinical Category C. Examples include, but are not limited to: Bacillary angiomatosis, Candidiasis, oropharyngeal (thrush)</td>
<td>Candidioidomycosis, disseminated, or extrapulmonary</td>
</tr>
<tr>
<td>Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy</td>
<td>Cryptococcosis, extrapulmonary</td>
</tr>
<tr>
<td>Cervical dysplasia (moderate or severe)/cervical carcinoma in situ</td>
<td>Cryptosporidiosis, chronic intestinal (greater than 1 month’s duration)</td>
</tr>
<tr>
<td>Constitutional symptoms, such as fever (38.5°C) or diarrhea lasting for longer than 1 month</td>
<td>Cytomegalovirus disease (other than liver, spleen, or nodes)</td>
</tr>
<tr>
<td>Hairy leukoplakia, oral</td>
<td>Cytomegalovirus retinitis (with loss of vision)</td>
</tr>
<tr>
<td>Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome</td>
<td>Encephalopathy, HIV-related</td>
</tr>
<tr>
<td>Idiopathic thrombocytopenic purpura</td>
<td>Herpes simplex: chronic ulcer(s) (greater than 1 month’s duration); or bronchitis, pneumonitis, or esophagitis</td>
</tr>
<tr>
<td>Listeriosis</td>
<td>Histoplasmosis, disseminated or extrapulmonary</td>
</tr>
<tr>
<td>Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess</td>
<td>Isosporiasis, chronic intestinal (greater than 1 month’s duration)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td></td>
</tr>
</tbody>
</table>

$^a$These conditions must meet at least one of the following criteria: (a) the conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity; or (b) the conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection

$^b$Once a Category C condition has occurred, the person will remain in Category C

### Table 2.5.2 The CD4+ T-lymphocyte categories$^a$ [9]

| Category 1: $>$500 CD4+ T-cells/µL |
| Category 2: 200–499 CD4+ T-cells/µL |
| Category 3: $<$200 CD4+ T-cells/µL |

*Categoryization is based on the lowest accurate CD4+ T-cell count, not the most recent one

### 2.5.3 Antiretroviral Therapy

Almost no other field of medicine has developed as rapidly as this and is evolving constantly.
After the introduction of highly active antiretroviral therapy (HAART), HIV-associated morbidity and mortality have dropped dramatically and opportunistic infections and HIV-associated tumors such as Kaposi’s sarcoma are seen less frequently.

Multiple prospective multicenter studies could show that a combination therapy is superior to monotherapy [15]. In Germany, 22 substances in six different classes are approved (Table 2.5.3) [14].

All symptomatic patients and all patients with less than 200/µL CD4+ cells (in repeated testing) should be treated with HAART. To patients with a CD4 cell count between 200 and 350/µL, HAART should be offered. In patients with higher CD4 cell counts, a viral load >50,000–100,000 is also a marker for faster progression. Before the beginning of HAART, a resistance testing can help to choose an optimized therapy [13, 16, 17].

Antiretroviral treatment has developed immensely within the last 15 years. In 1987, zidovudine monotherapy was the only therapeutic option. With the introduction of didanosine and zalcitabine in 1991 and 1992, a first combination of nucleoside analogs was possible [15]. Stavudine and lamivudine were registered in 1994 and 1995. A turning point was the introduction of the protease inhibitors (PI) saquinavir and indinavir in 1995 and nevirapine and the class of NNRTIs in 1996. This was the beginning of the HAART era. The combination of a “backbone” of two NRTI and a NNRTI or protease inhibitor still form the basis of antiretroviral therapy [13, 14]. Addition of low-dose ritonavir to PI (“booster”) results in a high plasma concentration of coadministered PI and decreases pill burden, number of doses, and food restrictions [18].

The drug treatment is monitored on a regular basis. After 2–4 weeks of HAART initiation, a safety assessment should be performed. The viral load should be at least 1 log lower than baseline. After 3–6 months, viral load should be undetectable. Any relapse should be a reason to confirm compliance and to consider drug monitoring or resistance testing. A change of viral replication of 0.5–0.7 log 10 is considered significant in patients with detectable viral load. The CD4 cell count should be controlled every 3 months. A change of 30% of the absolute result or 3% of the relative result is significant. Reasons for therapeutic failure can be drug interactions, resistance, or compliance problems. Antiretroviral therapy may interact with other medications (for example, antimycotics, macrolide antibiotics, St. John’s wort, and antacids) [14].

Multiple new substances have been approved lately. These include combinations of substances that are already in the market, for example, emtricitabine plus tenofovir plus efavirenz (FDA approved 7/2006, Atripla®). New substances of old classes that can be used in heavily pretreated patients are developed (for example, the NNRTI Etravirin (TMC 125 approved 1/2008)). Hopes for lesser side effects and better efficacy have risen for the class of integrase-inhibitors. Raltegravir (MK0518) is the first substance of this class and was approved in 10/2007 [19]. The CCR5 receptor antagonist Maraviroc (approved 10/2007) can only be used after tropism testing. Patients with CXCR4 tropic viruses do not profit from this treatment. The dose has to be adjusted according to the background therapy.

2.5.4 Experimental Approaches

During the last few years, the development of nucleoside analogs came to a halt. An exception is Apricitabine (AVX-754), which is chemically similar to lamivudine, but is still active when up to 5 NRTI mutations are present. Aveva is currently planning to enter Phase II b studies. A handful of other NRTI are in Phase I studies (for example, Elvucitabine, Fosalvudine, Fozivudine).

Rilpivirine (TMC 278) is effective against most NNRTI-resistant viruses. Its effectiveness is comparable to efavirenz, but with significantly less CNS side effects. Phase III studies are on the way. Other NNRTI (for example, GW5634 and BIRL 355BS) are in early phases of research. The development of many PI has been terminated due to increasing competition. New substances have to be effective against PI-resistant viral isolates and show minimal side effects. Vicriviroc is the second CCR5 receptor antagonist. This is currently tested in phase III studies. Cases of integrase inhibitor resistance have already been reported. It is not clear if the new substances of this class evitegravir and GSK 364735 are still active in raltegravir-resistant viruses. Attachment inhibitors and maturation inhibitors have just entered phase II studies.
### Table 2.5.3 Antiretroviral therapy

<table>
<thead>
<tr>
<th>Substance</th>
<th>Dose and Formulation</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudin (AZT, Retrovir®)</td>
<td>2×1 capsule à 250 mg</td>
<td>Neutopenia, anemia, myopathy, lipoatrophy, nausea, headache, fatigue</td>
</tr>
<tr>
<td>Lamivudin (3TC, Epivir®)</td>
<td>1×1 tablet à 300 mg or 2×1 tablet à 150 mg</td>
<td>Rarely diarrhea, neuropathy</td>
</tr>
<tr>
<td>Abacavir (ABC, Ziagen®)</td>
<td>1×2 tablets à 300 mg or 2×1 tablet à 300 mg</td>
<td>Hypersensitivity syndrome</td>
</tr>
<tr>
<td>Stavudin (d4T, Zerit®)</td>
<td>2×1 capsule &lt;60 kg à 30 mg &gt;60 kg à 40 mg</td>
<td>Peripheral neuropathy, elevated liver enzymes, lipodystrophy</td>
</tr>
<tr>
<td>Didanosin (ddI, Videx®)</td>
<td>1×1 capsule &lt;60 kg à 250 mg &gt;60 kg à 400 mg</td>
<td>Peripheral neuropathy, rarely pancreatitis</td>
</tr>
<tr>
<td>Tenofovir (TDF, Viread®)</td>
<td>1×1 capsule à 300 mg</td>
<td>Nephrotoxicity, hypophosphataemia</td>
</tr>
<tr>
<td>Emtricitabin (FTC, Emtriva®)</td>
<td>1×1 capsule à 200 mg</td>
<td>Headache, diarrhea</td>
</tr>
<tr>
<td><strong>NNRTI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevirapin (NVP, Viramune®)</td>
<td>14 days 1×1 tablet à 200 mg then 2×1 tablet à 200 mg</td>
<td>Rash, elevated liver enzymes</td>
</tr>
<tr>
<td>Efavirenz (EFV, Sustiva®)</td>
<td>1×1 tablet à 600 mg</td>
<td>Dizziness, nightmares, rashes, hypercholesterinaemia</td>
</tr>
<tr>
<td>Etravirine (TMC 125, Intelence®)</td>
<td>2×2 tablets à 100 mg</td>
<td>Rashes, nausea</td>
</tr>
<tr>
<td><strong>PI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saquinavir (SQV, INV, Invirase®)</td>
<td>INV: 2×2 tablets à 500 mg RTV: 2×1 tablet à 100 mg</td>
<td>Diarrhea, nausea, hyperlipidaemia</td>
</tr>
<tr>
<td>Indinavir (IDV, Crixivan®)</td>
<td>IDV: 2×2 capsules à 400 mg RTV: 2×1 tablet à 100 mg</td>
<td>Hyperbilirubinaemia, nephrolithiasis, paronychia, hyperlipidaemia</td>
</tr>
<tr>
<td>*Nelfinavir (NF, Viracept®)*³</td>
<td>NFV: 2×5 tablets à 250 mg</td>
<td>Diarrhea, meteorism</td>
</tr>
<tr>
<td>Lopinavir (LPV/r, Kaletra®)</td>
<td>2×2 tablets. à (200 mg LPV + 50 mg RTV fixed dose combination)</td>
<td>Diarrhea, meteorism, hyperlipidaemia</td>
</tr>
<tr>
<td>Atazanavir (ATV, Reyataz®)</td>
<td>ATV: 1×2 capsules. à 150 mg RTV: 1×1 tablet à 100 mg or 1×2 capsules à 200 mg</td>
<td>Hyperbilirubinaemia, ECG-changes</td>
</tr>
<tr>
<td>Fosamprenavir (FVP, Telzir®)</td>
<td>FPV: 2×1 tablet à 700 mg RTV: 2×1 tablet à 100 mg</td>
<td>Rashes, headache, diarrhea hyperlipidaemia</td>
</tr>
<tr>
<td>Tipranavir (TPV, Aptivus®)</td>
<td>TPV: 2×2 tablets à 250 mg RTV: 2×2 tablets à 100 mg</td>
<td>Nausea, rashes</td>
</tr>
</tbody>
</table>

(continued)
Table 2.5.3 (continued)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Dose and Formulation¹</th>
<th>Side effects²</th>
</tr>
</thead>
</table>
| Darunavir (DRV, Prezista®)       | DRV: 2 × 2 tablets à 300 mg  
RTV: 2 × 1 tablets à 100 mg | Diarrhea                           |
| Ritonavir (RTV, Norvir®)         | Used to booster other (PI/r)  
e.g.,  
RTV: 2 × 1 tablet à 100 mg | Hyperlipidaemia, elevated liver enzymes,  
nausea, diarrhea, perioral numbness |

Fusionsinhibitor

Enfuvirtid (T-20, Fuzeon®)        | 2 × 1 mL à 90 mg s.c. | Injection side reaction, bacterial pneumonia, hypersensitivity |

Integraseinhibitor

Raltegravir (RGV, MK 0518,  
Isentress®)                      | 2 × 1 tablets à 400 mg | Diarrhea, nausea, headache |

CCR-5 Antagonist

Maraviroc (Celsentri®)            |                       |                                    |

¹Sometimes, liquid formulation is also available  
²For further information, see summary of product information  
³Recalled from the European Union markets on 6th June 2007 due to unexpected contamination with ethyl mesylate

The effect of Interleukin 2 was investigated in the ESPRIT study. The study investigators found that the CD4+ T-cell counts of participants who received IL-2 rose an average of 160 cells/mm³ higher then those of participants in the control group. The incidence of HIV-associated opportunistic diseases and death was not significantly different for participants who revised IL-2 [20].

Treatment guidelines are updated almost annually in order to keep up with the scientific progress. There is still a need for new substances, considering resistance problems and long-term side effects [9].

2.5.5 Complications

2.5.5.1 Immune Reconstitution Syndrome

The immune reconstitution syndrome is still a challenge to therapists. Subclinical infections can demask after immune reconstitution, especially in patients with less than 200/µL CD4+ T-cells who start antiretroviral therapy. Before the beginning of therapy, a screening for opportunistic infections with chest X-ray, ultrasound of the abdomen, and a fundoscopy should be standard procedures. Patients have to be watched carefully during the first weeks of antiretroviral therapy [9].

2.5.5.2 Resistance

Shortly after the first antiretroviral substances were available, the problem of resistance was observed [21]. Many studies showed that an optimized therapy chosen after resistance testing leads to a better response rate. Resistance testing should be performed before the beginning of antiretroviral therapy and when a treatment fails. The current therapy should be continued during testing. Primary resistance has been seen in up to 14% of therapy-naive patients [16, 17, 22–24].

2.5.5.3 Drug Monitoring and Drug Interaction

Therapeutic drug monitoring helps to reassess compliance and reveals drug interactions or malabsorption. Sufficient plasma levels are essential for the
virological response. Toxicity can be caused by excessive drug levels. So far, only NNRTI and PI plasma concentration can be measured on a routine basis. Intracellular measurement of NRTIs has not been standardized [25].

Protein inhibitors are metabolized by the cytochrome p450 system. Multiple drug interaction with tuberculostatics, antidepressive agents including St. John’s wort, sildenafil, lipid lowering drugs, antymycotics, and antibiotics are known. Antacid drugs should not be coadministered with atazanavir because their resorption is pH dependent [26]. Methadone levels can be lowered. Dose adjustment is necessary to avoid withdrawal syndrome [27]. Severe drug reactions have been seen in combination with the H1 antihistamines terfenadine and astemizole. New antihistamines such as cetirizine and loratadine can be used [28]. Drug interaction should be considered individually (link: www.hiv-druginteractions.org). Therapeutic drug monitoring can be helpful.

2.5.5.4 Side Effects of Antiretroviral Therapy

The use of antiretroviral therapy is limited by side effects (Table 2.5.2). The mitochondrial toxicity of the old NRTIs is associated with lipodystrophy, hepatotoxicity, and other metabolic disorders [29]. Some side effects are substance specific, for example, zidovudin is known to cause macrocytic anemia [30] and abacavir associated with the hypersensitivity syndrome in HLA B5701-positive patients [31, 32]. Pancreatitis can be seen after treatment with didanosin [25] and tenofovir can cause nephrotoxicity [33]. Nevirapin can cause severe allergic skin reactions and liver toxicity, especially in women with high CD4 cell count [34]. The effects on the central nervous system of efavirenz can lead to dizziness, depression, and nightmares [35]. Gastrointestinal problems are often seen when PI are given. Hyperglycemia, lipodystrophy, and hyperlipidemia are also attributed to them [36]. Substance-specific side effects are nephrolithiasis and paronychia after indinavir treatment [37], and hyperbilirubinaemia during atazanavir treatment [38]. A good relationship and communication between the patient and the therapist can help minimize compliance problems due to side effects [9].

Take Home Message

> While fewer patients die from opportunistic infections, a growing problem in the manifestation of malignancies is witnessed. Increasing viral multidrug resistance, long-term toxicity such as lipodystrophy, osteoporosis, and cardiovascular disease are some other problems faced by HIV-infected patients in the subsequent years. HIV treatment is complex and changing constantly. Patients should be treated in specialized centers.

2.5.6 Global Variations

In developed countries, HIV infection is increasingly considered to be a chronic disease because of antiretroviral treatment, but worldwide treatment access has still not been established. Consequently, the worldwide epidemic has still not been stopped. It is essential that the UNAIDS/WHO 3 by 5 program launched in 2003 is fully conducted and extended. Additionally, mother-to-child transmission preventing programs must be intensified.

References

2.6.1 Ectoparasitic Infestations

2.6.1.1 Pediculosis

**Key Features**

- Knockdown resistance is related to voltage-gated sodium channels and is increasingly common among lice.
- Knockdown resistance can often be overcome by prolonged exposure to the pyrethroid.
- There is lesser resistance to malathion compared to other agents.
- Malathion efficacy is due, in large part, to the petroleum-based vehicle, which is irritating and flammable.
- Agents that kill via asphyxiation rather than neurotoxicity offer a better approach to treatment.

### 2.6.1.1.1 Etiology and Pathophysiology

Pediculosis is caused by sucking lice of the phylum Arthropoda, class Insecta, order Phthiraptera, suborder Anoplura, family Pediculidae, or family Pthiridae.

### 2.6.1.1.2 Clinical Characteristics and Diagnosis

Scalp itching and insomnia are common complaints. The diagnosis is established by the demonstration of lice or nits.

### 2.6.1.1.3 General Therapeutic Outline

Pyrethrins are widely available over the counter. Pyrethroids are the most commonly prescribed class of drugs. Malathion has a relatively small market share, but retains efficacy in most areas with drug-resistant lice.

### 2.6.1.1.4 Current Established Therapies

Pediculosis remains a widespread problem in both developed and developing countries. In developed countries, where treatment is readily available, resistance to available therapeutic agents is widespread. Gene mutations are implicated in knockdown resistance in lice, and lice with knockdown resistance frequently demonstrate resistance to permethrin, but not to malathion [1, 2]. Knockdown resistance is a manifestation of nerve insensitivity related to voltage-gated sodium channels. It manifests as a lack of immobilization of lice, but correlates with resistance to killing. Comparison of the cDNA sequence from different species shows highly conserved repeated domains in the sodium channel gene associated with resistance to pyrethroids [3]. When knockdown resistance occurs, a different therapeutic agent is generally appropriate. An alternative approach is to apply a pyrethroid for a prolonged period of time, which may still result in effective treatment.

---

D. M. Elston
Department of Dermatology, Geisinger Medical Center, 100 North Academy Avenue, Danville, PA 17821, USA
e-mail: Dmelston@geisinger.edu
Glutathione S-transferase-based (GST) resistance and monooxygenase-based resistance are also important mechanisms of resistance to pediculicides [4]. Synergism with enzyme inhibitors such as piperonyl butoxide suggests that enhanced monooxygenase-based metabolism exists. Comparative starch gel electrophoresis of louse enzymes is a promising tool to identify metabolic factors involved in resistance [5].

Commercial success of an agent, with widespread use, commonly correlates with the emergence of resistance to that agent. As a result, resistant lice are more common in developed countries where insecticides are used more widely. In one study, lice from the United States demonstrated resistance to a broad range of doses of permethrin, while lice from Borneo retained sensitivity to pyrethroids [6].

Permethrin resistance was first reported in Israel in 1994, manifested by a fourfold decrease in susceptibility to permethrin at the LT50 level [7]. Since then, resistance has become common in developed countries. Cross-resistance among pyrethroids is also common. In Buenos Aires, permethrin-resistant lice have demonstrated resistance to d-phenothrin and deltamethrin as well [8]. Synergism with the enzyme inhibitors piperonyl butoxide and triphenylphosphate suggests that enhanced metabolism may play a role in pyrethroid resistance in some locations. In Britain, d-phenothrin resistance was reported as early as 1994 [9]. Double resistance to permethrin and malathion has also been reported in Britain. Knockdown resistance accounts for the permethrin resistance, while esterase-based resistance is also common. In the Czech Republic, permethrin-resistant lice have demonstrated cross-resistance to d-phenothrin and bioaleurthrin. These lice remained susceptible to malathion and pirimiphos [11].

GST-based resistance is an important mechanism of DDT resistance. GST resistance occurred in Israel almost a decade before permethrin resistance, suggesting GST resistance does not confer cross-resistance to pyrethroids. Since then, various mechanisms of resistance have been reported among Israeli lice, including monooxygenase resistance and knockdown resistance [12].

Knowledge of the mechanism of resistance has therapeutic implications. Simultaneous treatment with agents with different mechanisms of action or simultaneous application of synergistic, allosterically coupled mixtures may delay or prevent the development of resistance. It may also be possible to replace an agent to which resistance was acquired by channel mutation with an agent to which increased susceptibility resulted from the same mutation [13].

Piperonal has been used as a pediculicide, but also exhibits a repellent action mediated by sensory organs in the tips of the louse’s antennae [14]. A spray formulation of 2% piperonal exhibited high repellency against body lice for 24 h.

Effective therapy requires either killing or removal of lice as well as ova. A uniformly effective agent does not exist. Therefore, mechanical means of removal must be coupled with any existing chemical agent. Topical agents that occlude the respiratory apparatus of the louse hold great promise for the treatment of lice. These agents offer the promise of low toxicity. Emergence of resistance to such agents is unlikely. At present, pyrethroids and pyrethrin combined with piperonyl butoxide retain a predominant market share for the treatment of lice. Malathion is also used, but the efficacy of malathion preparations is heavily dependent upon the vehicle.

### 2.6.1.1.5 Experimental Approaches

Immunization to lice appears promising. In a lab assay, rabbits immunized with louse extracts demonstrated resistance to infestation [15]. In sheep, immune responses to chewing lice reduced the size of the louse population [16]. Ultimately, the most effective and safest agents for the treatment of pediculosis will be those that kill by occluding the respiratory spiracles and asphyxiating the lice. Ova have a low oxygen requirement and will present a continuous challenge.

### 2.6.1.1.6 Complications to Avoid

Patients become frustrated with the lack of efficacy of prescription agents. They may resort to the application of flammable substances or essential oils that may produce contact allergy.
2.6.1.7 Global Variations

Carbaryl is also used in many parts of the world, but not in the United States.

2.6.1.2 Scabies

Key Features

- Pyrethroids react on voltage-sensitive sodium channels.
- A protracted sodium influx lowers the nerve action potential threshold, resulting in repetitive firing.
- At high concentrations, pyrethroids also act on GABA-gated chloride channels.
- Pyrethroids have a broad therapeutic index, but congenital leukemia has been reported after heavy abuse of permethrin during pregnancy.
- All close contacts must be treated.
- Crusted scabies may require systemic as well as topical therapy.

2.6.1.2.1 Etiology and Pathophysiology

Scabies is an infestation by the human itch mite, Sarcoptes scabei.

2.6.1.2.2 Clinical Characteristics and Diagnosis

Itching, excoriation, and burrows may be prominent in the web spaces, genitalia, breasts, and axillae. Diagnosis is established by the demonstration of the mite, ova, or feces.

2.6.1.2.3 General Therapeutic Outline

Scabies infestation is common, and spreads readily to close contacts [17, 18]. Hospitals, nursing homes, day-care centers, and prisons commonly experience scabies epidemics [19–23]. An adequate response to a scabies epidemic may require that many close contacts be treated. In one report, almost a thousand individuals required treatment in order to eliminate persistent scabies infestation in three nursing homes [24]. To prevent reinfestation, all close physical contacts must be treated simultaneously, regardless of the presence of symptoms.

Crusted scabies occurs in immunocompromised or debilitated patients, including patients with neurologic disorders, Down syndrome, organ transplants, graft-versus-host disease, adult T-cell leukemia, leprosy, and AIDS. The crusts and scales teem with mites, and patients are highly infectious.

Fomites are important in the spread of scabies, as evidenced by an outbreak of scabies among employees in a hospital laundry facility [25]. Bed linens should be washed after treatment for scabies. Vacuuming may also be of benefit, but the usefulness of environmental acaricides remains to be established.

2.6.1.2.4 Current Established Therapies

Permethrin is widely used in the United States and other developed countries [13, 26–28]. The main effects of pyrethroids are on voltage-sensitive sodium channels. A protracted sodium influx lowers the action potential threshold, repetitive firing. At high concentrations, pyrethroids can also act on GABA-gated chloride channels. All pyrethroids can exist as stereoisomers, each with different biological activities. They may be marketed as racemic mixtures or as single isomers. The mechanisms for pyrethroid toxicity are complex. Both piperonyl butoxide and organophosphates inhibit pyrethroid metabolism.

2.6.1.2.5 Experimental Approaches

Ivermectin, a macroclide endectocide with activity against both endoparasites and ectoparasites appears promising, but is not clearly superior to topical agents [29]. In the setting of widespread infestation in a prison setting, oral ivermectin at a dose of 300 µg/kg repeated for 7 days proved effective for both treatment and prophylaxis [30]. Lindane retains efficacy, while crotamiton has a lower cure rate than other available agents, and is best used as an antipruritic with some scabicidal effect.

There is potential for the development of an effective scabies vaccine. Sarcoptes scabiei cDNA demonstrates some homology with the house dust mite Euroglyphus maynei [31]. In dogs, serum IgG and IgE
responses to *Sarcoptes scabiei* var. Canis are exhibited during the cure of the first infestation, when dead mites are still present in the stratum corneum [32]. Proteins identified by antibody binding during challenge are candidates for inclusion in vaccines. There is some cross reactivity with dust and grain mite allergens. This is not surprising, considering the genetic homology between species. An experimental antiscabies vaccine based on soluble proteins failed to protect goats against sarcoptic mange. Vaccination invoked high levels of scabies-specific IgG but failed to induce specific IgE. In contrast, natural infection produced both strong serum IgE and strong IgG responses [33]. In a study of 78 patients with crusted scabies, eosinophilia and elevated IgE levels occurred in 58% and 96% of patients, respectively. Median IgE levels were 17 times the upper limit of normal, and yet did not provide protective immunity [34]. Assays of cell-mediated immunity may prove more valuable in evaluating potential scabies vaccines.

### 2.6.1.2.6 Complications to Avoid

Although it is generally well tolerated, congenital leukaemia has been reported after heavy abuse of permethrin during pregnancy [35]. The associated cytogenetic abnormalities could be recreated by permethrin in vitro. Fewer than ten deaths have been reported from ingestion or following occupational exposure to pyrethroids. Paraoesophia can occur, most commonly on the face. Pyrethroid ingestion can result in nausea and vomiting, mouth ulceration, and dysphagia. Coma and convulsions have been reported [36]. Neck dystonia has also been reported after the therapeutic use of permethrin [37].

Patients with crusted scabies are highly infectious and may infect many. Overuse or ingestion of lindane can produce seizures.

### 2.6.1.2.7 Global Variations

Precipitated sulfur [38], benzyl benzoate, and sulfiram are also used in many parts of the world.

### 2.6.2 Protozoan Infections

Protozoans are one-celled organisms. Those in the class Sarcodina move by means of pseudopods. Those in the class Mastigophora move by means of flagellae. Those in the class Ciliata move by means of short, hair-like cilia. Those in the class Sporozoa have no special organs of locomotion.

#### 2.6.2.1 Amoebic Infection

<table>
<thead>
<tr>
<th>Key Features</th>
</tr>
</thead>
</table>
| The major pathogens are *Entamoeba histolytica* and *Acanthamoeba*.
| Concurrent roundworm infections modulate the effect of antiparasite treatment on host cytokine responses.
| Treatment of entamoeba infections typically includes metronidazole.
| Abscesses must be drained.
| Disseminated cutaneous *Acanthamoeba* infections are commonly treated with 5-flucycosine and sulfadiazine.
| Tissue invasion is initiated by a lectin-mediated adhesion of the organism to target cells.
| Immunization against target antigens is promising as a therapeutic modality. |

#### 2.6.2.1.1 Etiology and Pathophysiology

The major amoebas that produce cutaneous infections are *Entamoeba histolytica* and *Acanthamoeba*. Concurrent roundworm infections modulate the effect of antiparasite treatment on host cytokine responses. Coinfected patients demonstrate diminished secretion of interleukin (IL)-5 and IL-12, but elevated IL-10. Thymus and activation-regulated chemokine (TARC) is elevated in patients with triple parasite infections. Effective treatment modulates the response. Following antiparasite therapy, secretion of IL-12 and IL-5 is increased, while TARC and IL-8 are substantially diminished [39].
2.6.2.1.2 **Clinical Characteristics and Diagnosis**

*Entamoeba histolytica* is primarily a gastrointestinal parasite, but cutaneous ulcers sometimes occur as a result of extension from an underlying amoebic abscess. Penile lesions may occasionally be sexually acquired. *Naegleria, Acanthamoeba,* and *Balamuthia sp.* are free-living organisms widely distributed in soil and water. They are important agents of fatal amoebic encephalitis [40]. *Acanthamoeba* and *Balamuthia* infections of the skin have been described in patients with AIDS or other forms of immunosuppression [41–43]. Central nervous system infection is commonly fatal. The diagnosis is made by the identification of the organisms in biopsy specimens, or by culture on a lawn of *E. coli* [44]. Indirect hemagglutination, gel diffusion precipitation tests, and counterimmunoelectrophoresis play supportive roles in diagnosis.

2.6.2.1.3 **General Therapeutic Outline**

Oral therapy and drainage of abscesses are the mainstays of treatment.

2.6.2.1.4 **Current Established Therapies**

Treatment of entamoeba infections typically includes metronidazole, 750 mg orally, three times a day for 10 days. Abscesses must be drained; otherwise, treatment may be ineffective. Disseminated cutaneous *Acanthamoeba* infections are commonly treated with 5-flucysine and sulfadiazine [45]. While some *Balamuthia* infections may respond to pentamidine, serious *Balamuthia mandrillaris* infections have required a combination of pentamidine, sulfadiazine, fluconazole, and clarithromycin [46]. Promising therapies for amoebic infection include complexes derived from pyridoxal and S-benzyl- or S-methylthiocarbamate. In vitro, these agents are more effective than metronidazole against *Entamoeba histolytica* [47].

2.6.2.1.5 **Experimental Approaches**

Tissue invasion by amoebic trophozoites is initiated by a lectin-mediated adhesion of the organism to target cells. Immunization against target antigens is promising as a therapeutic modality [48]. In an animal model, immunization with a tetramer of a pentapeptide isolated from *Entamoeba histolytica* protects against experimental amoebic liver abscess. The pentapeptide has demonstrated anti-inflammatory properties including the inhibition of monocyte locomotion. It may play a critical role in the establishment of infection, making it a suitable target for therapy [49].

2.6.2.1.6 **Complications to Avoid**

Failure to drain abscesses can result in failure of therapy.

**Take Home Message**

- Amebiasis can be treated effectively if the diagnosis is suspected and appropriate biopsies are obtained.

2.6.2.1.7 **Global Variations**

There is little global variation in treatment.

2.6.2.2 **Leishmaniasis and trypanosomiasis**

**Key Features**

- *L. tropica, L. major, L. aethiopica,* and *L. infantum* cause Old World cutaneous leishmaniasis.
- In the New World, *L. mexicana* and *L. braziliensis guyanensis* produce only cutaneous disease.
- *L. braziliensis braziliensis* and *L. b. panamensis* can result in mucocutaneous disease.
- New World leishmaniasis is commonly treated with pentavalent antimonial drugs.
- Old World disease can be treated with local hyperthermia, cryotherapy, intralesional sodium stibogluconate antimony, or emetine hydrochloride, or topical treatments such as paromycin sulfate with methylbenzethonium chloride.
- Heat therapy induces cytokine production similar to that observed in antimonial treatment.
2.6.2.2.1 Etiology and Pathophysiology

Cutaneous leishmaniasis is transmitted by sand fly bites. 

*L. tropica*, *L. major*, *L. aethiopia*, and *L. infantum* cause Old World cutaneous leishmaniasis. In the New World, *L. mexicana* and *L. braziliensis guyanensis* are thought to produce only cutaneous disease, while *L. braziliensis braziliensis* and *L. b. panamensis* can result in mucocutaneous disease.

2.6.2.2.2 Clinical Characteristics and Diagnosis

The major manifestations of Old World leishmaniasis are chronic ulcers and nodules. Mild visceral disease may also occur. Although New World disease may be purely cutaneous (Fig. 2.6.1), severe mucocutaneous disease may occur in the later stages with some New World organisms (Fig. 2.6.2). Disseminated cutaneous anergic leishmaniasis occurs in both New and Old World leishmaniasis.

2.6.2.2.3 General Therapeutic Outline

Old World disease may be treated with topical or intralesional agents or by means of destructive modalities. New World disease is more commonly treated with systemic agents because of the risk of mucocutaneous manifestations.

Current Established Therapies

Old World disease can be treated with local hyperthermia, cryotherapy, intralesional sodium stibogluconate antimony, or emetine hydrochloride, or topical treatments such as paromycin sulfate with methylbenzethonium chloride or even ketoconazole cream under occlusion. Localized radiofrequency heat has been used successfully to treat cutaneous leishmaniasis, but the most interesting observation in patients treated with targeted heat treatment is that untreated lesions also heal. The healing may result from a host immune response, as heat therapy induces cytokine production similar to that observed in antimonial treatment [50].

New World leishmaniasis is commonly treated with pentavalent antimonial drugs. Sodium stibogluconate is administered intramuscularly or intravenously at a dose of 20 mg/kg/day in two divided doses for 28 days.

2.6.2.2.4 Experimental Approaches

Other systemic medications are less well studied, and include ketoconazole, itraconazole, rifampin, dapsone, and allopurinol. Cutaneous lesions of Chagas’ disease in patients with cardiac transplantation have been successfully treated with allopurinol [51].

The addition of vaccine immunotherapy can reduce the total dose and duration of treatment [52]. Visceral disease caused by *Leishmania infantum* in the setting of HIV infection has responded to pentavalent antimonial salts, liposomal amphotericin B, and itraconazole. Several lipid-based formulations of amphotericin B have been used to treat leishmaniasis, especially in the face of...
resistance to pentavalent antimony compounds. Some cases refractory to amphotericin B have responded to oral miltefosine [53]. Recurrent cutaneous disease may require pentamidine and dapsone [54, 55]. Other useful agents include miltefosine and paromomycin. Resistance has emerged, and 60% of patients with visceral leishmaniasis in parts of India do not respond to pentavalent antimonials. The resistance mechanism appears to relate to thiol metabolism and drug efflux [56].

Immunoprophylaxis is a promising area of research. Leishmania major infection induces immunity, which is protective against reinfection. Studies in mice suggest that CD4+ T cells are responsible for the protective immunity. Implicated T cell populations include parasite-independent central memory T cells and parasite-dependent T effector cells. The existence of a long-lived population of memory T cells suggests the potential for effective vaccination strategies [57]. A subset of Leishmania major organisms lack GDP-mannose transporter. These organisms have been termed Deltalpg2 parasites. They have the ability to persist in the host long-term, but fail to induce clinical disease. In a mouse model, they induce protective immunity against more virulent L. major organisms. Unfortunately, effective therapy requires more than an attenuated strain of organisms. In mice, effective immunity requires coadministration of oligodeoxynucleotides, and parasite persistence alone appears insufficient to induce protective immunity [58].

Transfer of the interleukin-12 gene via plasmid to mice challenged with L. major results in a reduction of lesion size and a reduction in the number of parasites in draining lymph nodes. These changes are accompanied by a shift toward a Th1 cytokine profile. The IL-12 gene is also associated with enhanced immunity in T. cruzi infection. Anti-CD4 or anti-CD8 monoclonal antibodies can negate the protective effect. Mice depleted of natural killer cells are especially susceptible to infection, but transfer of the IL-12 gene restores immune-mediated resistance. These findings suggest that CD4+ and CD8+ T cells are critical for effective immunity [59].

A vaccine combining BCG with killed Leishmania promastigotes has been shown to be beneficial in some patients with New World cutaneous leishmaniasis. In mice, the BCG-Leishmania vaccine prolonged survival when given intraperitoneally 10 and 3 days before T. cruzi inoculation. The immunity was dependent upon IFN-gamma production [60].

Leishmania amazonensis, an organism typically associated with cutaneous leishmaniasis, has been shown in vitro to be susceptible to light-mediated cytolysis after treatment with aluminum phthalocyanine chloride [61]. This suggests the potential for various forms of photodynamic therapy. While Leishmania mexicana promastigotes and Leishmania major amastigotes can be inactivated by long-wavelength ultraviolet A (320–400 nm) light plus psoralen, neither component is effective when used alone [62].

Post-kala-azar dermal leishmaniasis may require daily injections of sodium stibogluconate for many months. Liposomal amphotericin B has proven effective in some refractory cases. A major benefit of liposomal formulations is the reduced potential for nephrotoxicity related to relative specificity for parasitized macrophages [63]. High concentrations of interleukin 10 in the blood is a risk factor for post-kala-azar dermal leishmaniasis, suggesting the potential for immunotherapy [64].

New therapies are on the horizon. Substituted quinolines may be effective against various forms of leishmaniasis and trypanosomiasis. As some have also shown promising antiretroviral activity, they may have a place in the treatment of leishmania/HIV co-infections [65]. More effective delivery systems for antiparasitic drugs include more than just liposomes and emulsions. Nanoparticles, bioadhesive macromolecules, and cochleates appear promising [66].

### 2.6.2.2.5 Complications to Avoid

Mucocutaneous disease.

#### Take Home Message

- Old World disease can be treated with topical therapy and physical modalities. New World disease typically requires parenteral therapy.

### 2.6.2.2.6 Global Variations

Antimony n-methyl glutamine is used in some countries.
References

56. V oorhis WC (2005) Leishmania inactivation in human platelets by a psoralen (amotosalenHCl) and long-wavelength ultraviolet irradiation. Transfusion 45(9):1459–1463
Part III

Papulosquamous Dermatoses
3.1.1 Etiology and Pathophysiology

Psoriasis is a chronic inflammatory skin disease of unknown etiology. The disease is inherited as a polygenic trait [1] and is characterized by epidermal hyperproliferation and markedly reduced epidermal turnover time with defective keratinization [2]. Psoriasis is associated with HLA-CW6 allele (PSORS1), but other genetic loci have been described [3, 108, 117]. Previously, the dissection of the pathophysiology was mainly focused on keratinocytes. Following the finding of marked efficacy of ciclosporin [4–6], the involvement of T cell was established.

Recent evidence suggests the involvement of both T cells and dendritic cells [7–9]. These may include Th1/Tc1, Th17 cells, and TNF-α and iNOS-producing dendritic cells. This concept is related to a remarkable effect of anti-TNF-α agents and anti-IL-12-, IL-23-p40 antibody [10]. The contribution of interferon-α producing plasmacytoid dendritic cells has also been proposed [9].

3.1.2 Clinical Characteristics and Diagnosis

Psoriasis is a chronic, recurrent, inflammatory skin disease characterized by circumscribed erythematous scaly papules and plaques. The lesions are of variable size, sharply demarcated, dry, and usually covered with layers of fine silvery scales. The lesions have a predilection for the scalp, nails, the extensor surfaces of the limbs, the elbows, the knees, and the sacral region. Skin folds may be predominantly affected (inverse psoriasis). Nail lesion includes pitting, onycholysis, subungual hyperkeratosis, etc. The eruption is usually symmetrical and may vary from a solitary lesion to numerous plaques. Subjective symptoms such as itching or burning may be present. Involution in the center of the lesion may result in annular and gyrate configuration.

Psoriasis may begin insidiously on the scalp or on the extensor surfaces of the elbows, and remain localized to the original region. Occasionally, the onset is more sudden and widespread; in still others, the first lesions may be limited to the fingernails. The mean age of onset is approximately 25 years, although it also develops sporadically in older persons, in whom it tends to have a milder course [11].
Koebner response is the appearance of the typical lesions of psoriasis at the sites of injuries. New lesions may be produced by scratching of the skin. Auspitz phenomenon is pinpoint bleeding from the capillaries of the skin when a psoriatic scale is forcibly removed. Characteristic histopathology includes (1) hyperkeratosis with parakeratosis within which collections of neutrophils may be present (Munro’s microabsscess), (2) absent or decreased granular layer, (3) psoriasiform hyperplasia with elongated rete ridges, (4) thin suprapapillary plates, (5) edema of the papillary dermis with dilated capillaries, and (6) moderate perivascular and interstitial infiltrate of lymphocytes. The typically angulated psoriatic epidermal architecture can be explained by marked proliferation of epidermal keratinocytes [12, 13].

The typical psoriasis is easily diagnosed by its characteristic clinical and histopathological findings. Differential diagnosis may include seborrheic dermatitis, pityriasis rosea, pityriasis rubra pilaris, eczema, psoriasiform syphilis, lichen planus, etc.

Plaque type psoriasis (psoriasis vulgaris) is the major form. It consists of 80–90% of psoriasis [14, 15]. There are several clinical variants.

Guttate psoriasis is characterized by numerous small, up to 1 cm, lesions over the body. It may be preceded by a streptococcal pharyngitis, particularly in children and in young adults. They are scattered more or less evenly over the body. Psoriasis vulgaris begins as the guttate form in 15% or more of cases [16].

Psoriatic lesions may be extensive and generalized forming erythroderma (psoriatic erythroderma). It consists of 1–2% of psoriasis, and may be precipitated by administration of systemic steroids.

Psoriatic arthritis is an inflammatory arthropathy associated with psoriasis and usually characterized by absence of rheumatoid factor. Up to 90% of patients with psoriatic arthritis may have nail changes.

Generalized pustular psoriasis is characterized by the presence of variable numbers of sterile pustules appearing in erythematosus and scaly lesions associated with constitutional symptoms. Several exacerbations may occur, and in the intervals between them, lesions of ordinary psoriasis may be seen. Four variants are (1) acute generalized pustular psoriasis (von Zumbusch type), (2) generalized pustular psoriasis of pregnancy (impetigo herpetiformis), (3) infantile and juvenile pustular psoriasis, and (4) subacute annular or circinate pustular psoriasis.

### 3.1.3 General Therapeutic Outline

Psoriasis usually requires lifelong intermittent treatment. Numerous treatment modalities are available (Table 3.1.1). The selection of the therapy depends on the situation of each patient, who might have various psychosocial problems, other complicating disorders, etc. Furthermore, the options of psoriasis treatment available are considerably different among different countries. Psoriasis patients are not always satisfied with their treatments; they generally prefer oral therapies to phototherapies and consider most adverse effects and several discomforts important for selecting treatment [17].

<table>
<thead>
<tr>
<th>Table 3.1.1 Treatments of psoriasis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topical Treatment</strong></td>
</tr>
<tr>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Active vitamin D3 analogs</td>
</tr>
<tr>
<td>Anthralin</td>
</tr>
<tr>
<td>Tazarotene</td>
</tr>
<tr>
<td>Tar</td>
</tr>
<tr>
<td><strong>Phototherapy</strong></td>
</tr>
<tr>
<td>Goeckerman therapy</td>
</tr>
<tr>
<td>Photochemotherapy (PUVA)</td>
</tr>
<tr>
<td>Systemic PUVA</td>
</tr>
<tr>
<td>Topical PUVA</td>
</tr>
<tr>
<td>Bath PUVA</td>
</tr>
<tr>
<td>Broadband UVB therapy</td>
</tr>
<tr>
<td>Narrowband UVB therapy (TL-01)</td>
</tr>
<tr>
<td>Balneophototherapy</td>
</tr>
<tr>
<td>308 nm excimer laser</td>
</tr>
<tr>
<td>[104, 105]</td>
</tr>
<tr>
<td><strong>Systemic treatment</strong></td>
</tr>
<tr>
<td>Methotrexate</td>
</tr>
<tr>
<td>Ciclosporin</td>
</tr>
<tr>
<td>Retinoids</td>
</tr>
<tr>
<td>Hydroxyurea</td>
</tr>
<tr>
<td>Fumaric acid esters</td>
</tr>
<tr>
<td><strong>Biologics</strong></td>
</tr>
<tr>
<td>Alefacept</td>
</tr>
<tr>
<td>Efalizumab :withdrawn in 2009</td>
</tr>
<tr>
<td>Etanercept</td>
</tr>
<tr>
<td>Infliximab</td>
</tr>
<tr>
<td>Adalimumab</td>
</tr>
<tr>
<td>ustekinumab</td>
</tr>
<tr>
<td><strong>Others</strong></td>
</tr>
<tr>
<td>Chinese herb medicine</td>
</tr>
<tr>
<td>Tonsillectomy</td>
</tr>
</tbody>
</table>
3.1.3.1 Quality of Life and Patient Satisfaction Rate for Treatments

The psoriasis patients have large handicap on their social occupational activities [18–20]. The impairment of the quality of life caused by psoriasis equals or even exceeds that due to other major illnesses such as diabetes, rheumatoid arthritis, and cancer [20]. In a US study among severe (covered 10% or more of their bodies) psoriatic patients, 79% had a negative impact on their lives, 40% felt frustrated with the ineffectiveness of their current therapies, and 32% felt that their treatment was not strong enough [18]. The patient satisfaction rate for the treatment in Japan is even less [19]. The QOL of family members and partners may also be affected [21]. A large discrepancy between physician’s evaluation and patients’ satisfaction rate has been documented; many patients are not satisfied with their treatments than the physician’s expectation. In this regard, PASI scoring alone is not a reliable predictor of the patients’ QOL [22].

3.1.3.2 Evaluation of Biologic Agents

Recently biologic agents show remarkable effects on psoriasis [23–25]. Alefacept, which gives relatively long remission [26], is the typical agent targeted for T cell function. Although the efficacy of alefacept has been established, its efficacy rate is not so high. Only a subset (20–25%) of patients revealed PASI 75 score improvement (the reduction of psoriasis area and severity index). Efalizumab, another agent that inhibits T cell function, shows considerable therapeutic efficacy in a subset (30%) of patients, too [27]. Efalizumab may show rebound phenomenon occasionally accompanied with pustulization. Efalizumab was withdrawn from the market in 2009 (vide infra).

Anti-TNF-α agents (infliximab, etanercept, and adalimumab) show a remarkable effect on psoriasis [28–30]. Recently, anti-IL-12, IL-23-p40 antibody (ustekinumab) showed a marked benefit even by a single administration [10]. Alefacept is also re-evaluated; it shows long-term remission on psoriatic arthropathy, when combined with MTX than MTX alone [31].

The main concern about the biologics is the long-term chronic immunosuppression, which may increase various infections (including tuberculosis) and the risk of cancer. So far these drugs have been well tolerated, but long-term safety data are essential. Paradoxically anti-TNF-α agents may cause psoriasiform eruption during the use for other rheumatic disorders [32]. Guidelines for biologics are available. British Association of Dermatologists guideline indicates the choice of three agents (etanercept, efalizumab, and infliximab) [25]. Etanercept should be considered first choice for patients with significant, uncontrolled psoriatic arthritis. For patients with stable psoriasis, wherein a decision has been made to treat with an anti-TNF agent, etanercept should be used unless there are clear reasons not to do so. Infliximab is useful in clinical circumstances requiring rapid disease control, e.g., in unstable erythrodermic or pustular psoriasis due to its very rapid onset of action and high response rate.

Guideline of American Academy of Dermatology shows detailed recommendations for five agents, alefacept, efalizumab, and anti-TNF agents (adalimumab, etanercept, and infliximab) [14].

3.1.3.3 Pathophysiologic Rationale of Psoriasis Therapy

Epidermal keratinocytes and/or T cells/dendritic cells are the targets of psoriasis therapy (Fig. 3.1.1). Active vitamin D3 analogs show main function by inhibiting keratinocyte proliferation [33]. Retinoid also targets the epidermal keratinocytes [34]. Lymphocytes but not keratinocytes are the main target of MTX and PUVA. The figure shows only the main target of each therapy and does not necessarily deny other effects; for example, ciclosporin, besides its effect on T cells, has an inhibitory effect on keratinocyte proliferation at higher concentrations. Active vitamin D3 analogs affect immunocytes shifting Th1 cytokine profile of plaques to Th2 cytokine profile [35]. Transcriptional repression of IL12, IL23p40 gene has also been reported [36].

Figure 3.1.1 suggests the rationale for combination therapy; good results would be expected by the combination of the therapy against different target cells rather than the same target. Examples of favorite combinations would be topical corticosteroids and active vitamin D3 analogs, and retinoid and PUVA (Re-PUVA).

For the treatment of psoriasis the systematic approach is essential [37, 38]. Choice of treatment for
Psoriasis depends on many factors, including the extent of disease, the patient’s QOL, and complications. To apply various therapies to each individual patient, algorithm flow chart approach based on the extent and severity of the lesion using PASI score may be used. However, PASI score may not necessarily indicate the patients’ perception against the disease.

The pyramid diagram [Fig 3.1.2] is the frame work of the psoriasis treatment modalities currently available in Japan [15]. Shared decision making by both physicians and patients is essential for the selection of the treatment modalities.

The new guideline of American Academy of Dermatology provides decision tree of the treatment option [14]. It indicates that deforming active psoriatic arthritis should be treated by anti-TNF ± MTX. For extensive psoriasis UVB/PUVA, systemic treatment, and biologics are the options. For limited psoriasis topicals/targeted phototherapy are recommended; in case of lack of effect the options for extensive psoriasis would be considered. It is stressed that patients with limited skin disease should not automatically be treated with systemic treatment if they do not improve, because treatment with systemic therapy may carry more risk than the disease itself.

3.1.4 Current Established Therapies

3.1.4.1 Topical Agents [107]

3.1.4.1.1 Topical Corticosteroids

Topical corticosteroids in appropriate strengths give quicker onset of action and better control of pruritus than other topical agents. However, for long-term maintenance use, topical corticosteroids are not the most ideal agents, because of the well-known risks of developing skin atrophy, adrenal suppression and
tachyphylaxis. Further, corticosteroids tend to result in a shorter remission time than other treatments such as Goeckerman therapy, PUVA therapy, etc.

3.1.4.1.2 Active Vitamin D3 Analogs

The natural active vitamin D3 is 1α, 25-dihydroxyvitamin D3 (calcitriol). The three synthetic analogs, calcipotriol, tacalcitol, and maxacalcitol, are used topically among different countries. Side effects include local irritation, which may affect up to 20% of patients. All have the potential to affect systemic calcium homeostasis with hypercalcemia and hypercalciuria. Thus, the restriction of the total amount used per week and monitoring serum and urinary calcium levels should be performed. Sequential therapy combined with topical corticosteroids and combination therapy with PUVA and UVB phototherapy results in good response. Since active vitamin D3 is inactivated by UVA, it is recommended that vitamin D3 is not applied until after phototherapy on the same day.

3.1.4.1.3 Topical Sequential Therapy of Psoriasis (Koo)

Sequential therapy is a concept whereby different antipsoriatic therapeutic regimens are employed in a deliberate sequence to maximize the initial speed of improvement while minimizing the long-term risk of maintenance therapy [39, 40]. It involves three critical steps. Step one is an initiation (or “clearing”) phase. Step two is the transition phase. Step three is the maintenance phase. An example of topical sequential therapy for psoriasis is as follows: (1) Initiation phase: Application of topical corticosteroid in the morning and active vitamin D3 analog in the evening. (2) Transition phase: the same combined treatment in the weekend but active vitamin D3 analogs twice daily in weekdays. (3) Maintenance phase: only topical active vitamin D3 application which will be continued until complete clearance. Our experience suggests that (while most patients can proceed to the transition phase) not all patients successfully move to the maintenance phase. Nevertheless, the concept of the ideal safe goal for topical agents of psoriasis therapy is very worthy, which is adopted in the pyramid diagram approach (Fig 3.1.2).

3.1.4.1.4 Anthralin (Dithranol) [41, 42]

Anthralin (dithranol) is among the prevalent topical agents for treating psoriasis worldwide. This is not available in Japan. The therapy starts with low concentrations (0.05–0.1%) and given once daily. To prevent autooxidation 1–2% salicylic acid is added. The concentration of anthralin is increased weekly up to about 5% until the lesions are resolved.

Short-contact treatment is an alternative mode of application. Higher concentrations of anthralin (1–5%) are applied to the lesions for a short period of time (usually 10–20 min) and thereafter washed off. Application time is increased weekly until the lesions have cleared.

Major side effects of anthralin are skin irritation. At higher concentrations, anthralin causes brownish discoloration of the surrounding skin and of clothing. This is due to the oxidation product of anthralin on the upper stratum corneum. Hair discoloration is another problem.

3.1.4.1.5 Tazarotene [43, 44]

Topical retinoid, tazarotene, mainly reduces scaling and plaque infiltration, with limited effectiveness on erythema. Tazarotene in a 0.05 or 0.1% gel or cream is effective in the treatment of chronic plaque psoriasis. Tazarotene may cause local irritation at the site of application.

3.1.4.1.6 Tar

Coal tar and wood tar have been used. These tars contain a lot of ingredients, most of which are not well defined. Carbazole might be a major component of the antipsoriatic activity of coal tar [45]. Combination of topical crude coal tar with UVB phototherapy is the classical Goeckerman therapy. This consists of daily application of 2–5% crude coal tar, combined with a tar bath and UV light, and has been used with significant effects. Possible risk of skin cancer has been a matter of controversy. Despite several negative results, there is at least one case-controlled study that shows increased risk of skin cancer in patients treated with high exposure coal tar and UV light therapy, than in those treated with smaller dosage therapy [46].
3.1.4.2 UV Phototherapy

3.1.4.2.1 Goeckerman Treatment and Broadband UVB

Goeckerman treatment (crude coal tar application followed by UV irradiation) is not currently used in Japan. Broadband UVB irradiation is effective for psoriasis, but the irradiation dose is somewhat difficult to tune and the broadband UVB therapy is rapidly substituted by narrowband UVB therapy.

3.1.4.2.2 PUVA (8-Methoxypsoralen (8-MOP) and UVA) Therapy [47–50]

PUVA (8-MOP and UVA) is the standard photochemotherapy. Topical PUVA (bath PUVA) therapy is much more prevalent in Japan. Guidelines are available [109, 113, 118, 119].

Oral PUVA Therapy

Standard oral dosage of 8-MOP is 0.4–0.6 mg/kg, given 2 h before irradiation. Initial dosage of UVA depends on skin types, from 0.5 to 3.0 J/cm². The UVA dosage is increased by increments, 0.5–1.5 J/cm² according to response. Treatment is given 2–4 times weekly. Once substantial clearance is achieved, the frequency of treatment can be reduced. During irradiation UVA-opaque goggles must be worn and for the remainder of that day, UVA-blocking sunglasses should be worn. PUVA does not increase cataract risk among persons using appropriate eye protection [51]. The total UVA dose should be less than 2,000 J/cm². Compared with narrowband UVB, oral PUVA therapy achieves clearance in more patients with fewer treatment sessions and results in longer remissions [52].

Topical PUVA Therapy

8MOP may be topically applied on the psoriatic plaque, which is followed by UVA irradiation. Typically 0.3% 8MOP is topically applied, which is followed by UVA irradiation within 2 h. Initial dosage of UVA is 0.1–0.3 J/cm², which is about one fifth of systemic PUVA. The UVA dosage is increased by 20–50% increments. Major advantage of topical PUVA therapy is the lack of systemic effects, such as gastrointestinal complaints, and the overall reduction of UV dose less than that required to those of systemic PUVA. Because of the troublesome time-consuming topical application of 8-MOP, bath PUVA therapy is now more prevalent for disseminated psoriasis lesions. Uneven pigmentation is another disadvantage of topical PUVA therapy, which can be avoided by bath PUVA therapy.

Bath PUVA Therapy

Typically 0.0002% 8MOP bath (40–42°C) is prepared and the patient bathes for 10 min. This is followed by an immediate UVA irradiation. Initial dosage of UVA is 0.2–0.5 J/cm². The UVA dosage is increased by 20–50% increments. Bath PUVA therapy provides for a uniform drug distribution over the skin surface, very low psoralen plasma levels, and quick elimination of psoralen from the skin, reducing the risk of accidental sunburns.

Adverse Reactions of PUVA Therapy

Sunburn reaction is the most common side effect. PUVA lentigines are common depending on the total irradiation dose. Skin carcinogenesis is the main concern especially for fair-skinned patients [53, 54]. Although certain studies failed to show a clear relationship between PUVA and tumor development, a long-term follow-up of a large US cohort has provided evidence for the carcinogenicity of PUVA. Thus simultaneous application of immunosuppressants is not recommended. PUVA may be of some value for generalized pustular psoriasis but success rate is much less than that of retinoid.

3.1.4.2.3 Narrowband UVB Therapy [55–58, 110]

Philips TL-01 fluorescent lamps emit a narrowband UVB at 311+2 nm. Irradiation with this source is superior to conventional broadband UVB, producing longer remissions, and a lower incidence of burning.
The effectiveness of narrowband UVB is slightly less than that of PUVA, but it is more convenient and possibly less carcinogenic. The combination of narrowband UVB with etretinate decreased the number of treatments and the UV exposure required for clearing. Twice weekly, three times weekly, and 4–5 times weekly treatments are adopted depending on response and outpatient inpatient condition.

**3.1.4.2.4 Balneophototherapy** [59]

This is popular in Europe, where concentrated salt-water baths together with artificial UVB-sources are used. Studies at the Dead Sea disclosed that highly concentrated salt water (more than 20%) together with UVB light is effective. Recent randomized controlled study, however, did not result in a significant improvement than narrowband UVB alone in clearance of psoriasis [60].

**3.1.4.3 Systemic Therapy**

**3.1.4.3.1 Retinoids** [61–64, 115]

*Etretinate and Acitretin*

Retinoid is the treatment of choice for generalized pustular psoriasis. Plaque type psoriasis (psoriasis vulgaris) may be less responsive and often is treated by a combination with other treatments, such as UV phototherapy (Re-PUVA therapy, acitretin-UV therapy) [65, 66]. The usual initial dosage of etretinate is between 0.5 and 1 mg/kg/day, and daily doses of 0.75–1 mg/kg/day are generally required. With the higher dosage level, side effects are inevitable. Etretinate is teratogenic and is strictly contraindicated in pregnancy. In Japan fertile women must maintain contraception during treatment and for 2 years (for 6 months in men) after cessation of treatment. Hyperlipidemia, liver dysfunction, radiographic skeletal changes may be seen. Dryness of the lips, nose, eyes, mouth, and vagina is a dose-related side effect. Exfoliative cheilitis and peeling of fingertips, and palms and soles are common. Burning sensation, pruritus of the skin and paronychia may be seen. The drug should not be used in children or in young women except in compelling circumstances. Eretinate has been superceded by acitretin, which has a shorter half-life in many countries but not in Japan. Low dose acitretin therapy (25 mg/day) seems to be better tolerated and associated with fewer abnormalities found after laboratory testing than high dose therapy (50 mg/day) [66]. Many adverse effects associated with acitretin therapy are dose dependent and may cause limitation of its usefulness [66]. Acitretin is particularly effective when used in combination with phototherapy (acitretin-UV therapy) [65].

**3.1.4.3.2 Ciclosporin** [4, 5, 67–69]

Ciclosporin is usually given to patients with sufficiently severe disease. Microemulsion formulation (Neoral), which provides a more predictable absorption following oral administration, is available. A twice daily oral regimen is recommended. An initial daily oral regimen is 2.5–5 mg/kg/day. Maintenance dosage should be reduced to minimum that allows adequate control. Intermittent short course treatment (average of 12 weeks duration) is recommended [67]. Duration of treatment should be kept below 2 years whenever possible. The most important side effects are dose-related hypertension and nephrotoxicity. Immunosuppression may increase the risk of skin cancer. Regular monitoring of blood pressure and serum creatinine levels is essential during ciclosporin therapy. Increase in serum creatinine to more than 30% above baseline requires the reduction of ciclosporin. It should be noted that a small number of patients may have normal serum creatinine levels but a diminished glomerular filtration rate (GFR), which indicates the renal dysfunction. Psoriasis patients treated with ciclosporin have a significantly higher risk of nonmelanoma skin cancer [114]. This increased risk, however, is observed exclusively in patients who have been exposed previously to PUVA therapy [67]. There is no significant increase in risk of nonskin cancer with ciclosporin therapy.

**3.1.4.3.3 Methotrexate** [70–72]

Methotrexate inhibits DNA synthesis by inhibition of dihydrofolate reductase. The main target of methotrexate
is now believed to be lymphocytes, but not keratinocytes. Oral therapy is given once weekly. The initial dose is 5–10 mg, followed by a gradual increase of 2.5–5 mg/week. The maintenance dose is usually between 7.5 and 30 mg/week. Daily regimens have been abandoned. Before treatment, renal, hepatic, and bone marrow function should be evaluated. If renal function is impaired, a reduced dosage may be given, because methotrexate is mainly excreted from urine. Routine liver function tests should be supplemented by a liver biopsy. This may be substituted by an assay of serum aminopropeptide of type III procollagen, an alternative of liver biopsy [73]. Anemia, leukocytopenia and thrombocytopenia are contraindications to methotrexate therapy. Toxic side effects include hepatotoxicity causing fibrosis and cirrhosis, and bone marrow suppression. Patients with diabetes type 2 are at high risk of developing liver fibrosis [74]. As is the case of ciclosporin, potential risk of skin cancer should not be ignored. Combined use of etretinate is not recommended because of the risk of hepatotoxicity.

3.1.4.3.4 Fumaric Acid Esters [75–77]

Systemic treatment with a mixture of fumaric acid esters has been used mainly in Germany. A defined mixture of fumaric acid monoethyl and dimethyl esters is now used. Therapy begins with a low strength formulation and is increased weekly for 3 weeks. Then therapy continues with a normal strength formulation that is increased weekly up to a maximum of 1.29 g/day. Dosage is usually adjusted to an individual level. Monitoring of hematology especially of leukocytes is essential. Liver enzymes and electrolytes should also be monitored.

3.1.4.3.5 Hydroxyurea [78, 79]

Hydroxyurea is an antimetabolite, which inhibits ribonucleotide reductase. Compared with MTX it causes less anorexia, nausea, and hepatotoxicity. Clinical response is slow. The reported satisfactory response rates range from 45 to 80%. Hydroxyurea may be effective when other systemic drugs have failed, but is a less potent antipsoriatic agent. Regimens should rarely exceed 0.5 g 3 times daily. Bone marrow suppression with leukopenia is a common side effect. Hydroxyurea-induced cutaneous vasculitis has been reported.

3.1.4.4 Biologics [25, 80, 81]

3.1.4.4.1 Alefacept

Alefacept is a fusion protein that contains the extracellular domain of LFA3, a ligand of CD2 molecule. Since CD2 molecule is strongly expressed on the memory-effector T cells, it inhibits the active memory T cell function. Also, apoptosis is induced to alefacept-bound T cells through natural killer cells. Alefacept is the first biologic agent approved for the treatment of psoriasis. It is administered via intramuscular injection. A dosing course comprises a 12 weekly administration of 15 mg. The onset of action is slow, and only 20–25% of treated patients revealed PASI 75 score improvement. The combined use of topical corticosteroid does not appear to provide substantial additional clinical improvement [82]. Alefacept, however, shows relatively long remission. It also shows good results with long-term remission for psoriatic arthritis, when combined with MTX [31].

3.1.4.4.2 Efalizumab

Efalizumab is a humanized monoclonal antibody that targets CD11a, a subunit of LFA-1, and inhibits the interaction of ICAM-1, which is required for the activation and mobilization of T cell by binding to LFA-1 of T cell [27]. Efalizumab is available as a subcutaneous self-administered preparation once weekly. A single 0.7 mg/kg SC dose followed by weekly SC doses of 1 mg/kg is recommended. Efalizumab is effective with around 30% of psoriasis patients achieving a PASI 75 response. Adverse reactions include flu-like symptoms, and thrombocytopenia. The major concern is the rebound of psoriasis and occasionally to a more severe subtype such as erythrodermic or generalized pustular psoriasis. Most of the patients who experienced a rebound phenomenon are nonresponders on discontinuation of treatment [80]. For the responders efalizumab seems to be well tolerated [83]. Efalizumab may be related to serious infection such as JC virus-
related progressive multifocal leukoencephalopathy [84], and was withdrawn from the market in 2009.

3.1.4.4.3 Etanercept [30, 85]

Etanercept, which is self-administered subcutaneously, is a fusion protein consisting of two TNF receptors fused to the Fc portion of human IgG antibody. This construct creates an exogenous TNF receptor and prevents excess TNF-α from binding to cell-bound receptors. This results in reduction in the amount of active TNF-α. A dose of 25 and 50 mg twice weekly is recommended [86]. Efficacy is dose-related, with 34 and 49% of patients receiving 25 and 50 mg twice weekly, respectively, achieving PASI 75 response. Adverse reactions include a transient injection site reaction, congestive heart failure exacerbation, and greater risk of developing antinuclear antibodies (ANA). Demyelinating diseases, albeit rare, are also reported. There is no convincing evidence for an increased risk of opportunistic infection or tuberculosis.

3.1.4.4.4 Infliximab [29, 87]

Infliximab is a monoclonal human and murine chimeric antibody that specifically binds to TNF-α. This is administered intravenously. The dose is 3–5 mg/kg at weeks 0, 2 and 6 [29]. Infliximab shows marked effect with 90% of patients becoming clear or minimally affected at 10 weeks following 5 mg/kg. Subsequent maintenance infusion is given at 8 weeks interval. The patients’ QOL is significantly improved [88]. It is also effective for psoriatic arthritis [89]. Side effects include nonspecific symptoms such as headache and diarrhea. Infusion reactions occurring during or within 1–2 h of treatment affect up to 20% of patients and rarely may result in anaphylactic shock. Screening for tuberculosis before starting therapy is important because infliximab may reactivate latent tuberculosis. It should be used cautiously in patients with congestive heart failure. The risk of malignancy including lymphoma should also be kept in mind. The long-term use of infliximab suggests that it may lose its efficacy over time. This phenomenon is primarily due to the development of anti-infliximab antibodies. This can be minimized by the combined use of infliximab with a small dose of methotrexate.

3.1.4.4.5 Adalimumab [90–92]

Adalimumab is a fully humanized monoclonal antibody IgG1 that specifically binds to TNF-α. Adalimumab is administered subcutaneously in a 40-mg dose every other week. It is also effective for psoriatic arthritis [93]. As with other anti-TNF-α agents, primary concerns are infection such as tuberculosis, malignancy, and development of ANA. Although US-FDA investigated the risk of malignancy with anti-TNF-α agents, including adalimumab, and concluded that there was no definitive causal relationship, monitoring for lymphoma is still warranted. Because of its fully humanized nature, the development of anti-adalimumab antibodies is expected to be lower than that of anti-infliximab antibodies.

3.1.5 Experimental Approaches

A human anti-IL-12/IL-23-p40 monoclonal antibody (ustekinumab) shows a marked effect [10] and is now available in Europe and USA.

Everolimus, a new rapamycin-derived macrolide used for heart and kidney transplant patients, has been shown to be effective on severe psoriasis [94]. “Selective” broadband UVB lamps (UV6 lamps), which have little emission <290 nm, show similar efficacy and might be a safer option in terms of carcinogenesis than narrowband UVB lamps [95].

Dialysis might be effective, where peritoneal dialysis might be more effective than hemodialysis [96].

3.1.6 Complications to Avoid

Any treatment of psoriasis has its own side effects, which should not be ignored by the physician. The benefits and risks of each therapy must be weighed carefully for each patient, and treatment individualized accordingly. Although recently developed biologics show remarkable effect, rare adverse events may occur. Reported clinical studies might be insufficiently powered to detect rare adverse events associated with the biologics. Adverse events seem to be rare in alefacept.
3.1.7 Global Variations

There is a racial difference in the prevalence of psoriasis, which may be related to HLA. The prevalence of psoriasis in Western Europe and Scandinavia is between about 1.5–3% [3, 11]. It is rare in the Mongoloid race (under 1%: around 0.3%), pure native Americans, Latin American Indians, and Eskimos [101]. A US study shows that the prevalence of psoriasis in Caucasians is 2.5%, and that of African Americans is 1.3% [102].

In Japan the prevalence of psoriasis is estimated to be 0.1% [15]. The Japanese survey also disclosed a unique sex ratio in which male patients were double that of female. In other countries, the gender difference is usually not recognized.

The manuscript was basically written in 2007. Because of the explosive advance of psoriasis therapy especially of the biologics, a significant number of valuable references could not be adopted at the time of the proof-reading in Oct. 2009.

References


42. Symposium on anthralin. 1981 Br J Dermatol 105 (Suppl. 20)


3.2.1 Etiology and Pathophysiology

In parapsoriasis, T cells dominate, and these cells may penetrate into the epidermis resulting in some disturbance of epidermal proliferation and keratinization. The etiology of parapsoriasis is not known. Many synonyms have been introduced, which, to some extent, express morphological or pathogenetic aspects: digital dermatosis, xantoerythroderma perstans, chronic superficial dermatitis, retiform parapsoriasis, poikiloderma atrophicans vasculare, clonal dermatitis, and patch stage of mycosis fungoides.

In parapsoriasis, most T cells are CD4+ [1, 2]. In large plaque parapsoriasis, the infiltrate is dense, and T cell clonality is observed in many cases [2, 3]. In small plaque parapsoriasis, T cell clonality is more seldom and less substantial. Although it has been suggested that the more frequent observation of T cell clonality in large plaque parapsoriasis could be attributed to the dense infiltrate, the association between large plaque parapsoriasis and T cell lymphoma has been clearly demonstrated. The distinction between large plaque parapsoriasis and digitiform parapsoriasis has been suggested to be clinically important as large plaque parapsoriasis may progress into cutaneous lymphoma and digitiform parapsoriasis may not. However, in a recent study, the benign nature of digitiform parapsoriasis was challenged, as an epidermotropic cutaneous T cell lymphoma was observed in 23.5% of cases of large plaque parapsoriasis against 15% of cases with digitiform parapsoriasis [4]. However, a cutaneous T cell clone was observed in 10.3% of cases of large plaque parapsoriasis but not in digitiform parapsoriasis. In this study, loss of CD13 expression was suggested as an early marker for transition to cutaneous T cell lymphoma. Another interesting observation is the increased expression of Toll-like receptors 2, 4, and 9 in cutaneous T cell...
lymphoma, whereas the expression of Toll-like receptors in parapsoriasis was normal [5].

The transition of parapsoriasis to cutaneous T cell lymphoma can be expected in 10% per decade [6, 7] in large plaque psoriasis. In those patients with clonal T cell growth, this percentage has been estimated to be 20% over 5 years [8]. The chance of development of T cell lymphoma from small plaque parapsoriasis is very low.

In pityriasis lichenoides, the infiltration of T cells and erythrocyte extravasation characterize the histopathological picture. In PLEVA, the epidermis shows edema and necrosis. In PLC, only some focal necrosis may be observed, and parakeratosis and epidermal hyperplasia are observed.

In PLEVA, CD4+ cells dominate, whereas CD8+ cells dominate in PLC [9, 10]. In a study on cytotoxic skin-homing CD8+ lymphocytes in T cell lymphoma pityriasis lichenoides and varicella zoster lesions, the CD8+ lymphocytes had a skin-homing CLA+ CCR4+ phenotype and strong production of antiviral protein MxA was found in all investigated disorders [11]. This observation suggests that a common antiviral response pattern may lead to aberrant skin recruitment of CLA+ CCR4+ cytotoxic T lymphocytes in pityriasis lichenoides and cutaneous T cell lymphoma. T cell clonality can be observed in PLEVA, although PLC may also show clonality to a lesser extent [12, 13]. T cell clonality in pityriasis lichenoides suggests that PLEVA and PLC are related to T cell lymphoproliferative disorders. Clinically, pityriasis lichenoides may develop into lymphomatoid papulosis. Transition into lymphomatoid papulosis can be seen and very seldomly an association between pityriasis lichenoides and cutaneous or extra cutaneous lymphoma can be seen. In lymphomatoid papulosis, CD30+ cells are numerous, which are absent in pityriasis lichenoides.

Small plaque parapsoriasis is characterized by up to nummular lesions, and signs of atrophy are missing. In some patients, the lesions are more longitudinal “digit like.” According to the classical view, small plaque parapsoriasis tends to have a prolonged course over years and only seldomly develops to cutaneous T cell lymphoma (mycosis fungoides). However, a 26-year follow-up of 105 patients with parapsoriasis revealed that 10% of patients with small plaque parapsoriasis and 35% of patients with large plaque psoriasis developed cutaneous T cell lymphoma with a median duration of 10 and 6 years, respectively [14].

Large plaque parapsoriasis also shows the above-mentioned characteristics. However, the lesions in general are larger than 5 cm diameter. The 5 cm rule is an imaginary discrimination between small and large plaque parapsoriasis. In large plaque psoriasis, however, signs of atrophy are seen, in particular, a “cigarette paperlike” wrinkling. More advanced presentations of atrophy are poikiloderma atrophicans vascularis, characterized by reticular hyperpigmentations and atrophy with telangiectasias. Poikiloderma atrophicans vascularis is not specific for T-cell lymphoma but is also a presentation of dermatomyositis and a genodermatosis such as Rothmund Thomson syndrome and dyskeratosis congenita. As indicated above, large plaque parapsoriasis progresses to mycosis fungoides in 10% per decade.

The differential diagnosis of small plaque type parapsoriasis comprises pityriasis rosea, psoriasis, drug eruptions and secondary syphilis. The differential diagnosis of large plaque parapsoriasis is psoriasis, drug eruption, radiodermatitis, and other disease entities with an expression of poikiloderma atrophicans vascularis.

Also in pityriasis lichenoides, there is a male predominance. In particular, children are affected. The clinical features of pityriasis lichenoides comprise a spectrum of acute and chronic manifestations. The acute manifestations are collectively designated as pityriasis lichenoides et varioliformis acuta (PLEVA). PLEVA is also indicated as “Mucha-Habermann disease.” Individual lesions resolve in a few weeks time, leaving a scar. The course of this disease tends to be chronic with recurrent crops. Active lesions are characterized by vesiculations and ulceration. The chronic manifestations are designated as pityriasis lichenoides chronica (PLC). The lesions are characterized by brown scaly papules. Individual lesions persist for weeks to months. The median duration was 20 months.

### 3.2.2 Clinical Characteristics and Diagnosis

Parapsoriasis is more common in middle aged to elderly people. The disease is more frequent in males. The lesions are composed of ill-defined erythematous patches, which are characterized by some scaliness. In general, the patches have a yellow–brown discoloration. In general the lesions are asymptomatic.
in patients with PLC and 18 months in patients with PLEVA [15].

In case PLEVA manifests with hemorrhagic necrosis, lymphomatoid papulosis, most likely, is the diagnosis. In that case, the condition may progress to a T cell lymphoma.

In case the lesion in PLEVA or PLC has a diffuse distribution, the course is relatively short (<1 year). However, a more distal distribution pattern indicates a more chronic course over several years.

### 3.2.3 General Therapeutic Outline

The evidence for therapeutic efficacy and safety of treatments for parapsoriasis and pityriasis lichenoides is rather modest and treatment recommendations are largely based on clinical experience, open studies and case-series. The general therapeutic outline for parapsoriasis and pityriasis lichenoides has been summarized in Tables 3.2.1 and 3.2.2.

#### 3.2.4 Modes of Action

Accumulation of T cells and hyperproliferation of T cell populations are the crucial pathological changes; therefore, treatments for parapsoriasis and pityriasis lichenoides are focussed on inhibition of lymphoproliferation and/or elimination of T cells. In this respect, topical treatments such as corticosteroids, tacrolimus, carmustine, coal tar products, photo (chemo) therapy, and systemic treatments such as retinoids, methotrexate and cyclosporin are important possibilities. In this chapter a brief description of these treatments will be provided.

#### 3.2.4.1 Current Established Treatments

The efficacy, safety and complications to avoid are presented in this section.

#### 3.2.4.2 Topical Corticosteroids

Potent and ultrapotent topical corticosteroids are widely used in parapsoriasis and pityriasis lichenoides. However, in widespread conditions such as small plaque parapsoriasis and pityriasis lichenoides the hazards of corticoid side effects should not be underestimated, including atrophy of the skin, dermatitis perioralis and adrenal gland suppression. In the more localized lesions of large plaque parapsoriasis, the use of topical corticosteroids is safer. However, large plaque parapsoriasis often requires more active treatments.

#### 3.2.4.3 Coal Tar Products

The use of coal tar products is highly variable across the world. However, in particular, for more itchy manifestations, the use of coal tar products may provide important relief. For localized lesions, crude coal tar can be used, and for the more widespread manifestations, coal tar solutions provide a more practical approach.

---

**Table 3.2.1 Therapeutic preferences for parapsoriasis**

<table>
<thead>
<tr>
<th></th>
<th>Small plaques</th>
<th>Large plaques</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical corticosteroids</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>Topical coal tar</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>UVB phototherapy</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Photo(chemo)therapy</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Retinoids photo(chemo)therapy</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>Topical carmustine</td>
<td>–</td>
<td>++</td>
</tr>
</tbody>
</table>

± = a less popular option; + = a regular option; ++ = a popular option

**Table 3.2.2 Therapeutic preferences for pityriasis lichenoides**

<table>
<thead>
<tr>
<th></th>
<th>PLEVA</th>
<th>PLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical corticosteroids</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Topical coal tar</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>UVB phototherapy</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Photo(chemo)therapy</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Retinoids photo(chemo)therapy</td>
<td>++</td>
<td>±</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

± = a less popular option; + = a regular option; ++ = a popular option
3.2.4.4 Photo(chemo)therapy

Photo(chemo)therapy is an important treatment option for parapsoriasis and pityriasis lichenoides. Recently, narrow band UVB (3–4 exposures per week) has been shown to be highly effective and safe in a series of 45 patients with small plaque parapsoriasis [16]. In fact, 73% of the patients reached complete clearing after a mean number of exposures of 29. In 51% of the patients, some degree of postinflammatory hyperpigmentation was observed. In pityriasis lichenoides, a complete response was observed in 93% of 29 patients [17], with 73% still free from relapse up to 38–58 months.

Photo(chemo)therapy is a first line treatment for large plaque parapsoriasis. Although large series are not available for the treatment of parapsoriasis with photo(chemo)therapy, its efficacy has been documented [18]. Also, the addition of a systemic retinoid to phototherapy or photo(chemo)therapy has been shown to augment the therapeutic responsiveness [19].

Long term efficacy of PUVA has been shown in parapsoriasis with an average complete remission period following treatment as long as 29.5 months [18]. Also, in longstanding pityriasis lichenoides, PUVA was shown to be effective in a case report [20].

3.2.4.5 Methotrexate

In parapsoriasis or pityriasis lichenoides, not responding to the above mentioned treatments, methotrexate may be indicated [23]. Evidence for the efficacy of methotrexate in these conditions, however, is restricted to case reports.

3.2.5 Experimental Approaches

Excimer laser (308 nm) has a wavelength close to narrow band UVB [21]. Efficacy has been described in cases of large plaque parapsoriasis, resulting in long term improvement. In particular, for treatment resistant plaques, excimer laser may be indicated, although evidence for efficacy so far is limited.

Retinoids, in particular acitretin, has been shown to increase the efficacy of phototherapy and photochemotherapy [19]. An interesting new development is the RXR-ligand bexarotene, which has been shown to be effective both as topical and systemic treatment in cases of lymphomatoid papulosis and cutaneous T cell lymphoma [22] and it may be speculated that bexarotene is effective in parapsoriasis and pityriasis lichenoides.

3.2.6 Global Variation

For diseases with virtually no evidence based studies on therapeutic efficacy, experience based medicine has provided rules for treatment. These rules may show considerable variation between different centers and different countries.

Topical corticosteroids and photo (chemo) therapy are well established approaches in all countries. Topical carustine and bexarotene are rather infrequent in Europe in contrast to the popularity in the United States of America.

Coal tar is the first choice in particular in those countries with limited resources.

3.2.7 In Conclusion

In particular, in large plaque parapsoriasis and to a lesser extent in pityriasis lichenoides, we have to be aware of the possibilities of a transition to T cell lymphoma. It is a challenge for the future to identify patients who are at risk for this transition and to treat them adequately.

References

tous mycosis fungoides and atrophic large-plaque parapsoriasis exhibit similar abnormalities of T-cell antigen expression. Arch Dermatol 124:366–372
3.2 Parapsoriasis and Related Disorders


Lichen planus (LP) is a chronic inflammatory skin disease that frequently involves mucous membranes and is characterized by an autoimmune attack on the epidermis by skin-infiltrating T cells. It affects 0.22–1% of the adult population with no gender predilection, although some studies found a predilection for women. The onset of LP occurs most commonly in middle-aged to elderly individuals [1]. The hallmark of LP is the presence of pruritic, flat-topped, polygonal, violaceous papules that favor the extremities. Histologically, a dense, band-like lymphocytic infiltrate is seen underlying an acantholytic epidermis with basal cell damage and hypergranulosis. Lichenoid eruptions represent a heterogeneous group of conditions that resemble idiopathic LP, clinically and histologically. Although the cause of LP remains obscure, progress has been made in understanding the environmental factors, such as viral infections and drugs that trigger the onset of the clinical disease. Thus, the presence of these factors should not be overlooked in the treatment of LP. As a consequence, treatment strategies depend primarily on avoidance of these environmental factors and modulation of the immune response so as to interfere with the function of skin-infiltrating T cells. In this review, we emphasize: (a) clinical features, (b) pathogenesis, and (c) treatment and treatment-related complications.

3.3.1 Clinical Features

It is generally accepted that LP presents in varying forms, and these include annular, atrophic, bullous, erosive, hypertrophic, and linear. The nails and mucous membranes, such as oral mucosa, are also affected in 10 and up to 75% of patients with cutaneous LP, respectively [1].

Key Features

- Lichen planus (LP) is a chronic inflammatory skin disease mediated by skin-infiltrating T cells with autoaggressive potential.
- Viruses, drugs, and contact allergens constitute environmental factors that can trigger the onset of LP.
- Memory T cells generated by a previously encountered virus could be cross-reactive with drugs, contact allergens, or alloantigens, and they are activated upon the recognition of these cross-reactive antigens to cause immunopathology.
- Treatment strategies of LP depend on avoidance of these environmental factors and modulation of the immune response so as to interfere with the function of skin-infiltrating T cells.
- The standard therapies for LP include topical and systemic corticosteroids, retinoids, antimicrobials and psoralen, and ultraviolet A. Oral ciclosporin and topical tacrolimus are safe and effective treatments for recalcitrant LP.
- Although biologics such as alefacept and efalizumab offer interesting novel alternative treatments, a prospective study with long-term follow-up is needed to evaluate the efficacy and safety.
These descriptive terms refer to the characteristics of the individual lesions, and not the course of the disease. It is not uncommon to observe these lesions simultaneously in the same person: more than one clinical form is frequently present at a time. The duration of the disease is dependent in part on the characteristics of the lesions, and spontaneous remission is infrequent in hypertrophic, oral, and nail LP. In particular, both oral and nail LP rarely undergo spontaneous remission.

The frequently involved sites also depend on the characteristics of the lesions: usually, the flexor surfaces of the wrists and forearms, the dorsal surfaces of the hands, anterior aspect of the lower legs are commonly involved sites (Fig. 3.3.2) [1]; in actinic LP, the lesions primarily involve sun-exposed sites of the forehead and face followed by the dorsal surfaces of the arms and hands; in atrophic LP, the most common sites are the lower legs; lesions frequently seen on the glans penis have an annular configuration; and hypertrophic LP are often seen on the shins or dorsal aspect of the foot. Oral LP appears in at least three forms: reticular, atrophic, and erosive. Patients with erosive form of the disease are typically symptomatic, with pain being the most common complaint [2]. Patients with oral LP should be examined for other mucosal lesions, such as genital lesions. Such mucous membrane lesions are more resistant to conventional therapies than cutaneous
lesions and malignant transformation of longstanding, nonhealing oral LP has been reported. Even in cutaneous LP, chronic erosive lesions are at risk of developing squamous cell carcinoma.

Koebner’s phenomenon can be seen, particularly during the early phase of the disease. As a result of the Koebner’s phenomenon in sites of scratching or trauma, linear lesions frequently occur. The papules often coalesce to form larger plaques that become centrally depressed and atrophic with residual hyperpigmentation over a period of time, often representing as atrophic LP or annular LP.

Earlier studies reported a high prevalence of chronic liver disease in patients with LP [1, 3, 4]: these studies suggested that when chronic liver disease is associated with LP, hepatitis C virus (HCV) is generally the cause of the liver disease.

### 3.3.2 Histology

The histologic picture of LP is fairly uniform and diagnostic despite its variable clinical presentations. A characteristic histological feature of LP is liquefactive degeneration of the basal cell layer intimately associated with a band-like lymphocytic infiltrate showing a marked epidermotropic tendency. Colloid bodies representing apoptotic keratinocytes are usually present in the lower part of the epidermis and the superficial dermis. The epidermis also shows hyperkeratosis without parakeratosis, focal hypergranulosis and irregular acanthosis with a “sawtooth” appearance.

Although the majority of cells in the inflammatory infiltrate are lymphocytes, mainly CD3+ T cells, there are conflicting data regarding the T-cell subsets: while some investigators showed that the cellular infiltrate contained an increased ratio of CD4+ to CD8+ T cells [5, 6], others found a predominance of CD8+ T cells, particularly in older lesions and those located in close proximity to degenerating keratinocytes [7, 8]. Epidermal Langerhans cells are usually increased in active lesions. In some biopsies, the interface injury is confined to a single or few rete ridges, particularly in the earliest phase. Follicular or acrosyringeal involvement may also be seen when early LP lesions can be biopsied: this does not represent the coincidental involvement of the follicular epithelium by lichenoid infiltrates of the surrounding skin. In particular, lesions of lichen planopilaris are characterized by an inflammatory cell infiltrate around the hair follicles even at the late stage.

In oral LP, lesions often show parakeratosis rather than hyperkeratosis, and the epidermis frequently becomes atrophic. A recent immunohistochemical analysis of oral and cutaneous LP lesions showed that a selective localization of cells expressing the full-blown cytotoxic phenotype (positive for perforin and granzyme B) is particularly evident in oral LP, particularly in erosive oral LP, the most severe clinical variant of oral LP [9].

### 3.3.3 Pathogenesis

Clinical observations have long suggested a temporal relationship between exposure to various exogenous agents and the development of LP. Among various exogenous agents, viruses, drugs and contact allergens are frequently suspected as the environmental factors that can trigger the onset of LP.

Of the many potential exogenous agents, recent studies have established an infectious trigger as the likely etiologic basis: attention has recently focused on the role of viruses, in particular, HCV. Of the various types of LP, the oral form is most commonly viewed as a manifestation of HCV infection. Indeed, the presence of HCV RNA in the oral LP lesions was confirmed with PCR technique [10], indicating a direct role of HCV in the development of these lesions. However, in some studies, HCV RNA was isolated from the oral mucosal tissue in patients with HCV infection, regardless of the presence of LP lesions: this does not support a strong association with HCV infection. On the other hand, Lazaro et al. [11] demonstrated that HCV infects keratinocytes from cutaneous LP lesions, and that viral RNA is translated in these cells as demonstrated by the HCV incorporated in the skin biopsies. Thus, there are no convincing data so far to support a direct pathogenetic role for HCV in LP, indicating that HCV alone is not sufficient for the development of LP. Probably, HCV itself would only represent a triggering factor necessary for immune system alterations, and an interaction with other factors is required. Indeed, a recent tetramer analysis shows that HCV-specific CD4+ and/or CD8+ T cells are present at high frequencies in oral LP lesions compared with the circulating compartment and suggest that they are involved in these lesions [12].
With regard to the role of other viruses in LP, human herpesvirus 6 (HHV-6) and HHV-7 DNA was specifically detected in oral and cutaneous LP lesions, respectively [13, 14], by in situ hybridization and PCR techniques. In addition, sporadic case reports showed that LP lesions developed in areas previously affected by recent herpes simplex (HSV) or varicella-zoster virus (VZV) [15]. The presence of viral DNA in the LP lesions, however, cannot be taken as proof of causation of the disease: viral DNA from a past infection might persist in the lesions or irrelevant viruses might enter the lesions as part of a systemic infection.

Drugs are also the cause of LP lesions in some patients by virtue of lesional onset following initiation of drug therapy, and resolution or significant improvement following discontinuation of the implicated drugs; however, recurrence of the lesions following rechallenge with the implicated drugs has not been documented for the majority of these drugs. There is usually a latent period of several months from drug introduction to the appearance of the cutaneous eruption, while the latent period for conventional drug eruptions is usually 1–2 weeks; and the time course between lesional resolution and drug withdrawal is also several weeks to months, a time frame which is much longer than in conventional drug eruptions. The most commonly implicated drugs are ACE inhibitors, thiazide diuretics, antimalarias, quinidine, β-blockers, gold and penicillamine [1]. Because there are no established clinical or histologic criteria for reliably distinguishing drug-induced LP from idiopathic LP, a thorough search should be made to identify any relevant medications. In general, clinical manifestations and histological findings of drug-induced LP would be more polymorphic and atypical than conventional LP.

Contact allergy to a variety of metals has been shown to be important in the pathogenesis of oral LP [16, 17]. The metals that aggravate oral LP include amalgam (mercury), copper, palladium, beryllium, and gold. Positive patch test reactions to inorganic mercury compounds identify a subset of oral LP patients who have a high probability of benefiting from removal of amalgam dental restorations. However, previous studies also demonstrated that the vast majority of patients with oral LP showed improvement after the removal of amalgam fillings, regardless of patch test results to amalgam and other inorganic mercury compounds [17], suggesting that the removal of additional factors such as bacterial infections may contribute to the improvement.

### 3.3.4 LP as a Manifestation of Chronic Graft-Vs.-Host Disease (GVHD)

Lichenoid chronic GVHD closely resembling idiopathic LP, clinically and histologically, occurs 100 days or more after bone marrow transfer (BMT). There are two usual presentations of chronic GVHD, a lichenoid and a sclerodermatous form. The increasing use of peripheral blood rather than marrow and the early withdrawal of posttransplant immunosuppression have reduced the incidence of acute GVHD but have been associated with an elevated risk of developing chronic GVHD. Mucous membranes are often affected as manifested by lacy white plaques and erosions of oral mucosa, a finding indistinguishable from oral LP.

Interestingly, several studies demonstrated that reactivation of the herpesviruses precedes GVHD [18, 19], as suggested in LP. These findings could be interpreted as indicating that lichenoid GVHD as well as LP can be triggered or exacerbated by reactivations of these herpesviruses. How do viral infections or reactivations trigger the development of lichenoid GVHD or LP? How do the observations described above fit with a scenario of T-cell activation in response to drugs, contact allergens, or alloantigens in these conditions? The most likely explanation is that memory T cells generated by a previously encountered virus could be cross-reactive with these antigens and activated to cause immunopathology. In this regard, the herpesviruses are perhaps the most likely to be involved because they induce and maintain a potent specific memory T-cell response due to their common properties of ubiquitous prevalence in latent form in human populations. Because previous studies demonstrated that virus-specific T cells are nonspecifically trapped within inflamed sites [20], they would be trapped and expanded at inflamed skin sites and mediate tissue damage upon a cross-reaction with either self-antigens, drug-antigens or HLA molecules, even in the absence of their cognate viral antigens. This possibility is supported by a recent study that virus-specific T cells generated in response to a viral infection restricted to sites outside the liver can trigger T-cell-mediated “collateral damage” despite the absence of viral antigen in the liver [21]. This scenario provides an explanation for why LP lesions often appear at the sites where nonspecific insults such as trauma is supplied, a finding known as Koebner’s phenomenon.
3.3.5 Treatment

Withdrawal and avoidance of administration of causative or suspicious drugs are the mainstay treatment options for the management of LP, when a drug-based etiology is suspected. Although withdrawal of the offending drugs theoretically results in complete resolution, great variability in the clinical course has been reported. As described above, the lesions may persist for a long period of time following withdrawal of the drug. Conversely, even if the offending drug is not discontinued, drug-induced LP lesions sometimes disappear or appear intermittently [1]. These findings indicate that additional factors are also involved, and the presence of the offending drug represents only one factor necessary for the development of the eruption. Concomitant viral infections would represent such additional factors that may create some biologic alterations in the immune system sufficient to increase the risk of the development of LP.

Because spontaneous remission of cutaneous LP has been observed in up to two-thirds of patients after 1 year, it is difficult to exactly evaluate the efficacy of different forms of therapy in cutaneous LP. In contrast, the reported mean duration of oral LP is approximately 5 years and the erosive form rarely spontaneously resolves [22]: this form is often painful and chronic with unpredictable and frequent exacerbations. Therefore, current clinical trials of treatments for LP are usually restricted to managing the erosive form of oral LP.

3.3.5.1 Conventional Therapies and Their Complication

The standard therapies for LP include topical and systemic corticosteroids, topical and systemic retinoids, antimicrobials, psoralen plus ultraviolet A (PUVA) and antihistamines. First-line agents in the treatment of LP remain topical corticosteroids sometimes supplemented by a variety of other immunosuppressive agents as described below. Although topical corticosteroids are most commonly used for mild cases, it should be noted that the efficacy of topical corticosteroids in LP has rarely been systematically evaluated in randomized controlled clinical trials (RCT) and those trials tend to have small study numbers. Intrallesional corticosteroids or corticosteroids under occlusion are sometimes used for treatment of hypertrophic LP. Oral LP may benefit from inhaled forms of corticosteroids. In severe, acute form of LP, systemic corticosteroids remain a commonly employed intervention. The minimal effective daily dose of prednisone for treating LP is usually 15–20 mg [1]; treatments can be continued for 2–6 weeks and then gradually tapered over several weeks. Once systemic corticosteroids have started, drug dose should be reduced slowly so as not to cause rebound and relapses. Long-term maintenance therapy with systemic corticosteroids, however, should be avoided. One study demonstrated that the median time to clearing was 18 weeks in the corticosteroid-treated group and 29 weeks in the placebo group [23].

Long-term (3–6 months) administration of griseofulvin was shown to result in complete improvement in 86% of patients with LP [24], although the methods used in this study were not completely detailed and do not allow for definitive conclusions. In particular, the erosive form of oral LP has responded favorably to this drug. A complete response or significant improvement of generalized LP (mean duration of disease: 3.5 months) was observed with metronidazole, 500 mg twice daily for 20–60 days [25]. Oral sulfasalazine extensively used in inflammatory bowel disease has been shown to be useful in cutaneous LP: sulfasalazine administered in increasing doses from 1.5 to 3 g/day for at least 4 weeks was effective for cutaneous LP but not for LP of the mucosa [26]. This drug also helped in early elimination of the pruritus associated with LP lesions. Its efficacy was not associated with severe side-effects, such as dyspepsia, skin rash, or headache, while previous reports curiously showed the appearance of cutaneous or oral LP as a complication of sulfasalazine therapy in patients with inflammatory bowel disease [27] and rheumatoid arthritis [28]. Because the drug has no major adverse effects, it may constitute an interesting alternative to treatment with systemic corticosteroids. Because the drug has been shown to inhibit expression of some cytokines and adhesion molecules, these inherent immune dysregulating properties may have exerted opposite effects on T-cell activation depending on the state of activation and differentiation.

Acitretin is the only systemic retinoid that has a relatively good level of evidence regarding its efficacy in the treatment of cutaneous LP [23]. A therapeutic regimen consisting of 30 mg q.d. acitretin for 8 weeks resulted in significant improvement or
remission in 64% of those in the treatment group, compared with 13% in the placebo group. Acitretin has also been shown to be effective in treatment of imatinib-associated lichenoid eruption [29]: imatinib is a tyrosine kinase inhibitor used to treat chronic myeloid leukemia and imatinib-related adverse events include severe epidermal necrolysis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, a GVHD-like drug reaction and lichenoid eruption. Two patients who developed lichenoid mucocutaneous eruptions at 1–3 months after starting imatinib therapy were successfully treated with oral acitretin 25 mg daily, enabling continuation of the effective imatinib dosage. We also successfully used etretinate (50 mg q.d.) to treat patients with the acute, exanthematous form of LP, although we did not totally exclude the possibility of spontaneous resolution. In general, retinoids tend to be used for recalcitrant cases and relapse may occur after discontinuation of the drug. Thus, long-term maintenance therapy may be required.

### 3.3.5.2 Immunosuppressant Agents and Their Complications

Ciclosporin and tacrolimus are immunosuppressant agents that act directly on cells of the immune system, with a preference for T cells [30]. Oral ciclosporin is useful for inducing a remission in severe cases resistant to retinoids and systemic corticosteroid therapy [31, 32]. A complete response was observed with doses of ciclosporin ranging from 1 to 6 mg/kg q.d. In general, mucosal and genital lesions are somewhat less responsive and require higher doses [30]. Although the majority of patients did not experience a relapse during a follow-up period of several months, long-term use of the drug may be associated with renal toxicity and hypertension and the potential for development of nonmelanoma skin cancer. Previous studies demonstrated that ciclosporin-associated renal toxicity was related to drug dose and duration of therapy: it occurs almost exclusively during prolonged exposure to drug doses above 5 mg/kg q.d. [33]. Increases in blood pressure as well as renal toxicity may occur with long-term ciclosporin therapy and their regular monitoring is therefore needed for reducing these risks. These changes, however, are reversed following dose reduction or withdrawal of ciclosporin therapy. There is continuing controversy as to whether topical ciclosporin is effective for treatment of oral LP [34, 35]: although some investigators reported the effectiveness of topical ciclosporin for treatment of atrophic and erosive oral LP, many believed that this effectiveness was attributable to systemic absorption.

In contrast to ciclosporin, topically applied tacrolimus penetrates the skin in variable amounts. Therefore, topical tacrolimus preparations can be used for several inflammatory skin diseases to minimize the risk of systemic toxicity. There have been many recent reports of the successful use of topical tacrolimus, especially for erosive oral LP. To demonstrate the efficacy of topical tacrolimus in LP, several controlled studies have been conducted and found tacrolimus to be effective in reducing the symptoms of oral and vulvar LP unresponsive to more conventional therapies [36–38]. Most patients experienced symptomatic improvement in less than 1 month following twice-daily application of 0.1% tacrolimus ointment to oral lesions. The median relapse time was 5 weeks, ranging from 2 to 20 weeks. However, many patients required intermittent therapy to prevent subsequent flares, although significant number of patients remained in remission after stopping treatment. Long-term use (>1 year) did not result in any serious adverse effects: a systemic effect was not apparent in patients who required maintenance therapy and symptoms of burning resolved with continued use of the ointment. Treatment with topical tacrolimus also completely resolved the oral LP-like chronic GVHD lesions after 2 months of therapy and no flare-ups have been seen since then. Fortunately, the compound would penetrate the epithelium much less after the lesions have improved due to the anti-inflammatory activity of topical tacrolimus. This limits the potential side-effects of the long-term use. Topical tacrolimus ointment was also effective in controlling the symptoms of vulvar LP which are more severe and recalcitrant to conventional treatment as compared with oral LP.

Nevertheless, due to concern that local immunosuppression of the skin may lead to an increased incidence of skin infections, one should be cautious in using tacrolimus ointment for extended periods, particularly when viral triggers are highly suspected. Indeed, there have been case reports of viral infection associated with topical tacrolimus for a 1-year history of LP of the labia minora [39]: despite no recollection of previous episodes of genital HSV lesions, the clinical complications...
picture of the HSV lesions was not consistent with a primary HSV infection but favored reactivation of previously asymptomatic or dormant HSV. The risk of using tacrolimus topically with respect to carcinogenesis in erosive oral LP lesions thought to be more prone to develop into cancer has been of some concern, although the premalignant potential of oral LP has been a controversial issue for the past several decades [40]: the range of malignant transformation of oral LP is between 0.04% and 1.74%. Recently, the US Food and Drug Administration (FDA) has resulted in a warning that the use of topical calcineurin inhibitors may be associated with an increased risk of cancer based on animal studies and case reports. Although the causal relationship between topical use of tacrolimus and the development of a squamous cell carcinoma is uncertain in a recent case report [40], it should be kept in mind that topical immunosuppressant drugs have the potential carcinogenic effect which may go beyond mere immune suppression: they may have an impact on cancer signaling pathways. Nineteen cases of cancer were reported in patients treated with topical tacrolimus: nevertheless, because the cancer was diagnosed 21–790 days after the start of therapy, causative associations are unclear. Although it is unclear whether there is an increased attributable risk of cancer due to tacrolimus therapy given the known increased risk of cancer in erosive oral and vulvar LP, it should be of note that the majority of the cancer occurred at the sites of the drug application. Thus, because of the potential increased risk of malignancy and the lack of long-term data, continued safety monitoring is necessary in patients who are being treated with these immunosuppressant drugs. Pimecrolimus, closely related in structure and activity to tacrolimus is also known to be effective for the treatment of oral LP, although pimecrolimus exerts less local immunosuppressive effect than tacrolimus.

Mycophenolate mofetil (MMF), a new immunosuppressive agent which specifically and reversibly inhibits the proliferation of activated T cells, was also reported to be effective in the management of disseminated, erosive, hypertrophic bullous LP and lichen planopilaris in anecdotal reports. Oral MMF may be preferable to other immunosuppressive drugs like ciclosporin because of its safer side-effect profile. Patients treated with these immunosuppressive agents, particularly those with erosive and ulcerative lesions, should undergo careful follow-up evaluation.

### 3.3.5.3 Phototherapy and Its Complication

Significant improvement has been observed after bath or systemic PUVA in patients with resistant long-standing LP. However, the risk of promoting carcinogenesis, especially in patients with skin type I and II, has to be balanced against the benefits. Phototherapy would accelerate carcinogenesis in the skin when applied after the skin had been pretreated with immunosuppressant agents, such as tacrolimus. The usefulness of PUVA has prompted evaluation of extracorporeal photopheresis (ECP) for recalcitrant LP. One case series demonstrated that erosive oral LP cleared in all seven cases after an average of 24 sessions of ECP (two consecutive days per month), and follow-up at 24 months revealed no recurrences [41]. Ultraviolet A1 (UVA1) has also been shown to be effective in the treatment of therapy-resistant LP which was exacerbated during PUVA therapy. The use of narrowband UVB with a peak emission at 311 nm has also been reported to be effective in recalcitrant LP. In many patients, complete and partial clearance occurred after 30 exposures (mean cumulative dose: 17.7 J/cm²) [42]. The operational 308-nm radiation of the excimer laser, photobiologically similar to its neighboring 311-nm wavelength was used for the treatment of oral LP unresponsive to conventional therapies and was found to have excellent efficacy. Remission time ranged from 2 to 17 months. Of note, the only poor responder in the study had chronic active HCV infection.

### 3.3.5.4 Biologics and Its Complication

Alefacept is a fully human dimeric fusion protein that interferes with lymphocyte activation by binding to the lymphocyte antigen CD2 and induces T-cell apoptosis via natural killer cell-induced granzyme release [43]. A dramatic response to alefacept therapy has been observed in two patients with long-standing, recalcitrant, generalized, and oral LP who showed no evidence of spontaneous resolution [44]: a 12-week intramuscular course of alefacept (15 mg/week) was initiated and significant improvement was seen within 4 weeks. After 12 weeks, both patients were almost free of new lesions. Neither of these patients reported any adverse events associated with alefacept therapy. The rapid
onset of action in these patients suggests a more direct role for the CD4+ T cells in the pathogenesis of LP as compared with psoriasis, in which the onset of action was usually delayed for 8–12 weeks after starting therapy.

Efalizumab is a recombinant humanized monoclonal IgG1 antibody that binds to CD11a, the α subunit of LFA-1; LFA-1 expressed on the surface of T cells plays an important role in T-cell activation and migration to the skin. Significant improvement of oral LP lesions was seen after 5 weeks of efalizumab therapy (an initial dose of 0.7 mg/kg, followed by a dosage of 1.0 mg/kg/week), with further improvement at 10 weeks [45]. Although none of the patients in these studies has serious side-effects, the long-term consequences of these therapies in patients with LP are unknown. A recent report describes a case with oral erosive LP who experienced drug-induced subacute cutaneous lupus erythematosus (SCLE) from the efalizumab [46]: 8 weeks after the initial injection of efalizumab, this patient developed a new rash consistent with SCLE. This patient demonstrated improvement after discontinuation of efalizumab. In addition, it remains unknown whether immunosuppressive therapy such as tacrolimus can be used concomitantly with these biologics. Although these biologics offer interesting novel alternative treatments for recalcitrant LP, a prospective study with long-term follow-up is needed to evaluate the efficacy and safety of these biologics in the treatment of LP. It should also be appreciated that T-cell recruitment to the skin is critical for host defense and that the T-cell might be helping the patient to rid themselves of the invading pathogens.

3.3.6 Global Variations

It appears that there are different views on the treatment of LP in different parts of the world. In Japan, the search for causative or suspicious drugs and metals that may aggravate LP is the first option for the management of LP. This trend does not appear to be apparent in other countries, particularly in the USA and Europe. Topical corticosteroids remain the mainstay treatment for cutaneous LP in all parts of the world. In recent years, there are considerable data supporting the efficacy of topical tacrolimus in the treatment of oral LP recalcitrant to topical corticosteroids in many countries. Although topical pimecrolimus offers a similar but less therapeutic potential than topical tacrolimus, this drug is more frequently used for the treatment of LP in Europe than in the USA and Japan: pimecrolimus has not been licensed in Japan. In general, dermatologists in the USA appear to be much more enthusiastic about the use of biologics including TNF blockade. In view of the recent observation that defects in numbers and effector functions of CD4+ CD25+ regulatory T cells (Treg) exist in autoimmune diseases and can be reversed by TNF blockade, we could use TNF blockade for restoration of Treg function in LP [47].

3.3.7 Complications to Avoid

We would like to emphasize the notion that the first therapeutic option for LP is elimination of causative or suspicious drugs and allergens such as metals. The long-term use of immunosuppressant agents, particularly biologics, should be avoided in these cases only for preventing symptoms. Because of the potential increased risk of malignancy and infections and the lack of long-term data, topical immunosuppressant agents, such as tacrolimus, and biologics such as efalizumab, should not be used for the long-term treatment of erosive oral or vulvar LP lesions that are difficult to clinically distinguish from carcinomas. Reactivation of tuberculosis and invasive fungal infections has been reported in patients receiving biologics. Thrombocytopenia has also been reported to develop in patients treated with efalizumab.

3.3.8 Conclusions

Although great strides have been made in the treatment of LP and in our understanding of the pathogenesis, existing therapeutic options are still insufficient, especially for the treatment of oral and vulvar LP with the premalignant potential. There is a temptation to borrow drugs that have been shown to be beneficial in other inflammatory skin diseases such as psoriasis and atopic dermatitis for the treatment of LP. Although therapies with combinations of immunosuppressive agents may be worth pursuing, the long-term efficacy and safety of these therapies should be carefully monitored in large number of patients.
3.3 Lichen Planus

Take Home Messages

- Identification and avoidance of administration of causative or suspicious exogenous agents are the mainstay treatment options. The role of drugs has to be carefully investigated.
- For mild cases, conventional therapies including topical corticosteroids are most commonly used.
- Treatments used in patients with more recalcitrant LP include oral retinoids, oral corticosteroids, and oral ciclosporin.
- Recently, several controlled studies have found topical tacrolimus to be effective in reducing the symptoms of oral and vulvar LP recalcitrant to more conventional therapies. Nevertheless, due to the concern that local immunosuppression of the skin may lead to an increased incidence of skin infections and cancer, one should be cautious in using immunosuppressant drugs for extended periods.
- Existing therapeutic options are still insufficient, especially for the treatment of oral and vulvar LP with the premalignant potential.

Acknowledgments The study was supported in part by grants from the Ministry of Education, Sports, Science, and Culture of Japan (to T.S.) and the Ministry of Health, Labor and Welfare of Japan (to T.S.).

References

Atopic Dermatitis and Related Diseases
Atopic Dermatitis
Andreas Wollenberg and Thomas Bieber

4.1

4.1.1 Definition

Atopic dermatitis (AD) is a common, clinically defined, chronic, and highly pruritic skin disease with a high impact on national economy and quality of life [1]. Although the definitions of most experts in the field are overlapping, there is no worldwide accepted definition of AD, and new efforts of harmonization are published every few years. The latest is from 2004, when a consensus group of the World Allergy Organization (WAO) proposed a revised terminology for atopy, as defined only in association with IgE-sensitization, leaving atopy only to be used in the context of documented allergen specific IgE antibodies in serum or with a positive skin prick test [2]. Hence, the medical term AD/eczema should be reserved to an eczematous condition with the typical lesions and associated to IgE-mediated sensitization. This latest terminology replaces the former term of extrinsic AD and includes only those patients who fulfill the above mentioned criteria. A substantial group (20–30%) of affected patients shows clinical signs of AD, but no IgE-sensitization at all [3]. According to WHO, the term “nonatopic eczema” (formerly intrinsic AD) should be applied for this group. Both forms, atopic and nonatopic eczema could be related in terms of natural history of the disease, since the condition may start as a nonatopic form and subsequently evolve into an atopic form, once sensitization has occurred.

4.1.2 Etiology and Pathophysiology

4.1.2.1 Epidemiology

AD has clearly increased by two to threefold (now the incidence is 15–30% in children and 2–10% in adults) during the past three decades in industrialized countries [4]. It usually starts during early infancy and childhood but may also persist or start in adulthood. In 45% of children, the onset of AD occurs during the first 6 months of life; however, more than 50% of these children do not display any sign of sensitization in the
first 2 years of life though suffering from classical skin lesions. The prevalence of AD in rural areas and in nonaffluent countries is significantly lower, emphasizing the importance of lifestyle and environment in the mechanisms of atopic disease. The propensity toward atopy-associated diseases may be due to a reduced microbial exposure in early life. This has been proposed as the “hygiene hypothesis,” [5] a concept which is hotly debated currently [6].

4.1.2.2 Genetics

AD is a paradigmatic genetically complex disease involving gene–gene and gene–environment interactions [7–9]. A genetically determined intrinsic epidermal barrier defect and immunological abnormalities, as well as environmental factors are required to generate the chronic skin inflammation underlying both forms of eczema. Parental atopy, in particular AD, is significantly associated with the manifestation and severity of early AD in children [10]. Other parental atopic diseases such as allergic asthma or allergic rhinitis seem to be less important in the development of AD, thus suggesting the existence of AD-specific genes.

Genetic linkage studies have identified several chromosomal regions linked to the epidermal barrier function (e.g., on chr. 1q21), and genetic variants mainly linked to candidate genes of the immune system (such as cytokines, chemokines and their receptors) have been additionally detected [11]. Most importantly, it has been shown that 2 loss-of-function mutations of the profilagrin/filaggrin gene (FLG) (R510X and 2282del4), a key protein in terminal differentiation of the epidermis, seem to be important risk factors for extrinsic AD, especially in combination with sensitization and asthma [12–14]. These variants seem to be more associated to the true AD form. It is expected that other yet-to-be-defined genetic variants from epidermal structures such as those localized in the epidermal differentiation complex (EDC) on chr. 1q21 may also play a role in these phenomena [15]. These genetic findings provide an important support for the well known impairment of the epidermal barrier observed in AD patients and could also deliver further clues to the natural history of the disease, i.e., the transition of a nonatopic eczema to an atopic eczema due to a facilitated penetration of allergens during chronic inflammation.

4.1.2.3 Immunological Mechanisms

Innate as well as adaptive immune mechanisms play a major role in the pathophysiological puzzle of AD. The former one is able to promptly react to almost all kinds of microbial colonization and attacks but is also involved in the initiation of the more specific but slower mechanisms of the adaptive immune response. Epithelial cells of the skin and cells residing at the interface with our environment are equipped with highly conserved recognition structures, the so-called pattern recognition receptors (PRRs) such as the Toll-like receptors (TLRs). These TLRs can bind a variety of microbial structures due to highly conserved microbial surface molecules, the so-called pathogen associated molecular pattern (PAMP). The binding of microbial products to cell surface of epithelial cells leads to cell activation, ultimately resulting in the production of newly described molecules with antimicrobial activities: the antimicrobial peptides (AMPs) [16]. In human skin the major AMPs are cathelicidin (LL37) and the human beta defensin 1, 2 and 3 (HBD1, HBD2 and HDB3). It has been shown that the strong colonization of AD with Staphylococcus aureus (which can trigger/enhance inflammation in an allergen independent way by the secretion of superantigens/enterotoxines) and the higher risk to develop wide spread viral infections (eczema herpeticum) are due to a downregulation of AMPs secondary to the particular inflammatory micro-milieu [17, 18].

AD is characterized by multiple alterations of the adaptive immune system. A predominant systemic Th2 dysbalance with increased IgE levels and eosinophilia are the hallmarks in this condition, while only eosinophilia is seen in nonatopic eczema [19]. Interestingly, Th2 profile is only detected in early/acute lesions of AD while chronic lesions rather have a Th1/Th0 pattern. Thus, chronic AD is not a classical Th2 disease but rather a biphasic disease [20]. Another unsolved question is the role of reported Th1-mediated apoptosis of keratinocytes [21], since apoptotic cells are more observed in acute lesions with Th2 profile and not in chronic lesions.

The role of T cells with regulatory activities (Tregs) in AD has been addressed recently [22]. Tregs form a complex family of cells with distinct surface markers but all expressing the nuclear factor Foxp3 which is mutated in the so-called IPEX syndrome (immune dysregulation, polyendocrinopathy, enteropathy, X-linked)
227

4.1 Atopic Dermatitis

Interestingly, staphylococcal superantigens subvert the function of regulatory T-cells and may thereby augment skin inflammation [24]. Much interest has been focused recently on the role of chemokines in the recruitment of inflammatory cells in the skin. Thus, MCP-4/CCL13, RANTES/CCL5, MIP-4/CCL18, TARC/CCL17, PARC/CCL18, MDC/CCL22, eotaxin/CCL11, and I-309/CCL11 have been shown to be involved in the development of acute and chronic skin inflammation as well as in the amplification of allergic reactions to bacteria or allergens [25].

The role of dendritic cells (DC) in AD has been extensively discussed elsewhere [26]. While myeloid (mDC, e.g., Langerhans cells (LC) and inflammatory dendritic epidermal cells (IDEC)) have been found in large amounts in lesional skin of AD, plasmacytoid dendritic cells (pDC) are almost absent which is in contrast to other inflammatory skin diseases such as allergic contact dermatitis or lupus erythematosus. LC and IDEC both express the high affinity receptor for IgE (FcεRI) in lesional skin, but not in normal skin. While LC are present in normal skin, IDEC are detected mainly in inflamed skin. LC and IDEC play a central role in the uptake and presentation of antigens or allergens to T cells and most probably also to regulatory T-cells. Interestingly, FcεRI-expression is detected on LC from normal skin during active flares of other atopic diseases such as allergic asthma or rhinitis, while FcεRI+ IDEC are confined to lesional skin. The role of LC in the initiation of the inflammatory reaction in AD is still unclear since they are active in priming naive T-cells into T-cells of Th2 type but produce only few amounts of proinflammatory cytokines. In contrast, IDEC which lead to a switch to Th1 response and secrete high amounts of proinflammatory signals may contribute to the amplification of inflammation. In atopy patch test, high numbers of IDEC invade the epidermis 72 h after allergen challenge.

pDC play a major role in the antiviral defense mechanisms by secreting type I interferons, i.e., IFN-α and -β. The absence of pDC in skin of AD [27] might contribute to their susceptibility toward viral skin infections such as herpes simplex-induced Eczema herpeticum. In contrast to LC and IDEC, pDC seem to constitutively express FcεRI even in nonatopics, but FcεRI expression is further up regulated in AD patients. Activation of this receptor leads to a decrease in the secretion of type I interferons [28].

4.1.2.4 Autoallergens

The majority of sera from patients with severe AD contain IgE antibodies directed against human proteins [29] and these IgE seem to appear very early in the history of the disease [30]. Some of these IgE-reactive autoantigens have been identified by cloning from human cDNA expression library obtained from epithelial cells. A particular representative is the structure designated Hom s 1, which is a 55-kDa cytoplasmic protein in skin keratinocytes [31]. Interestingly, most of these autoantigens are intracellular proteins, suggesting that release of these autoallergens from damaged tissues (by scratching) could trigger IgE- or T-cell-mediated responses. Thus, while IgE immune responses are initiated by environmental allergens, allergic inflammation can be maintained by human endogenous antigens in patients with severe AD. FcεRI expressing DC could be instrumental in these mechanisms.

4.1.3 Clinical Characteristics and Diagnosis

Nonatopic and AD are clinically not different and develop on dry skin which may in some instances resemble mild form of ichthyosis. Intense pruritus is also a common feature of both forms of eczema. The clinical spectrum of AD is wide, ranging from mild forms such as pityriasis alba to major forms with erythrodermic variants [1, 32, 33]. The eczematous lesions are polymorphic, with acute (oozing, crusted, vesicles or papules on erythematous plaques), subacute (mainly excoriated plaques), and chronic (lichenified and excoriated plaques) forms. Although pruritus can occur throughout the day, it generally worsens during the night and can profoundly alter the quality of life of the patient and its family.

Clinical patterns usually vary with age. First signs of inflammation typically occur during the third month of life and infants present with facial and patchy or generalized body eczema. Usually, the first lesions appear on the cheeks and are characterized by dry and erythematous skin with papulo-vesicular lesions. The term “milk crust” or “milk scurf” refers to the occurrence of yellowish crusts on the scalp which resemble scalded milk. At higher age, the inner and outer parts
of the arms and legs may also be affected (Fig. 4.1.1). The diaper area is usually spared. Itching and scratching are intense and promote the tendency to bacterial infection—mainly by *Staphylococcus aureus*. In childhood, sites of predilection of eczema are flexural areas, dorsum of the feet and hands. They can either develop from the preceding neonatal phase or arise de novo. Rashes usually begin with papules that become lichenified. The skin around the lips may be inflamed and constant licking of the area may lead to small, painful cracks in the perioral skin. For unknown reasons, AD may enter in more than 60% of the cases into complete remission during puberty.

As in childhood phase, localized inflammation with lichenification of the flexural areas is the most common pattern of adult AD. Predilection sites are the neck, upper chest, large joint flexures, and back of the hands. Facial skin is usually affected on the forehead, eyelids, and perioral region. Scalp involvement is possible and may even lead to diffuse hair loss. In adulthood, dry skin continues to be a persistent problem even if the inflammation has resolved. This becomes relevant especially in winter months. In adults, minimal variants of AD may occur such as hand dermatitis, nummular eczema, inflammation around the eyes, lichenification of the anogenital area, cheilitis sicca, nipple eczema or Pityriasis alba.

### 4.1.4 General Therapeutic Outline

The therapy of AD relies on a combination of daily emollient use and proper skin care, together with an anti-inflammatory therapy on an “as needed” basis and the avoidance of allergens and trigger factors relevant for the patient [34]. The emollients are chosen to match the dryness of the patient’s skin, the weather conditions, daily activities and contact allergies of the patient. The anti-inflammatory therapy will be chosen from a wide variety of topical corticosteroids with different strength and a selected range of topical calcineurin inhibitors (Table 4.1.1). Oral antihistamines, broad spectrum and narrow band UV-B as well as many other drugs and remedies may be added if certain conditions are met [34]. Cyclosporine, oral corticosteroids, azathioprine, mycophenolate mofetil, methotrexate and certain biologicals are restricted to the most severe cases (see below). We prefer educating the patients to handle the daily decisions of topical anti-inflammatory therapy themselves, but want to see our patients back on a regular schedule and in addition, if any severe flare up or infection is suspected.

### 4.1.5 Current Established Therapies

*Emollients* are the mainstay of AD therapy and must be chosen individually for every patient [34]. There is no such thing as one optimal emollient for every AD patient. As a rule, creams can be applied more easily than ointments, but the therapeutic effect of ointments lasts longer. Urea may be added to a formulation in up to 10% for adults and 2% in younger children, but the “stinging effect” of urea in minimally affected skin
2.1 Atopic Dermatitis

areas restrict the liberal use. Antiseptic substances such as triclosan may be added to a formulation in up to 2% and will reduce the skin colonization with *Staphylococcus aureus*. The key advantage of the topical antiseptic substance triclosan over topical antibiotics such as fusidic acid is that bacterial resistance to antibiotic drugs develops frequently, whereas this is not the case for antiseptic substances.

**Topical corticosteroids** are the anti-inflammatory substance group that is most frequently used in AD treatment. This is mainly due to their relatively low price and the fact that they are available in a wide variety of different strength and different formulations. The most relevant side effect following topical steroid overuse is skin atrophy of the epidermal and dermal layer. The wanted anti-inflammatory effect, which may be measured in erythema reduction, and the unwanted atrophogenic effect can be separated up to a certain extent by modern substances with an improved risk-benefit ratio [35]. Topical corticosteroids should be tapered out instead of an abrupt discontinuation [34]. This is recommended to reduce the otherwise high risk of a rebound phenomenon. We prescribe topical corticosteroids very often in all age groups and educate the patient that the unwanted side effects – which are well known to the public – can be avoided by cautious use of the drug.

The *topical calcineurin inhibitors*, tacrolimus and pimecrolimus inhibit the production of many proinflammatory cytokines dependent on the nuclear factor of activated T cells [36]. This leads to a rapid reduction of the erythema and itch sensation present in AD. Due to their mode of action which is different from that of corticosteroids, calcineurin inhibitors cannot cause epidermal or dermal skin atrophy [37]. This is a key advantage for treatment of AD lesions present in the face and especially the eyelid region. Tacrolimus ointment is more effective in AD than pimecrolimus cream, and may actually be used as a monotherapy for AD [38]. Major disadvantages are the higher price compared to corticosteroids and a burning sensation which is observed in up to 70% of patients after the first application of the drug [36]. We use topical tacrolimus and pimecrolimus very frequently in all patient ages including small children, but we do not combine it with any kind of UV-therapy. Tacrolimus ointment has recently been licensed for proactive therapy.

**UV-B light** has been used with great success as an addition to topical corticosteroids for many years in AD [39]. A novel type of narrow band light source emitting only UV-B light with a wavelength of about 311 nm has increased the efficacy, safety and acceptance of this therapy throughout Europe. UV-B is not suitable as a monotherapy and must be combined with topical corticosteroids to achieve complete remission of the disease [39]. This may be explained by the insufficient penetration of UV-B into the deeper layers of the dermis. We use UV-B therapy quite frequently but restrict the use of this therapy to patients over the age of 16 years.

**UV-A light** must either be applied in ultra high doses of up to 130 J/cm [2] to be really effective – which is still considered an experimental therapy – or it must be combined with photosensitizing substances such as 8-methoxy- Psoralene [39]. The latter PUVA-therapy is highly effective in AD but is time consuming, needs either oral intake of 8-MOP or a bath in 8-MOP containing water and increases the risk of skin cancer for the patient. We are quite restrictive with PUVA therapy.

<table>
<thead>
<tr>
<th>Table 4.1.1</th>
<th>Therapeutic considerations in atopic dermatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard care performed permanently</strong></td>
<td>even if no lesions are present</td>
</tr>
<tr>
<td>Daily use of emollients</td>
<td>Bathing with bath oil or shower twice per week</td>
</tr>
<tr>
<td>Avoidance of identified individual trigger factors and allergens</td>
<td>Wet wraps with emollients</td>
</tr>
<tr>
<td>Wet wraps with unperfumed tea</td>
<td>As needed</td>
</tr>
<tr>
<td><strong>Topical anti-inflammatory therapy</strong></td>
<td>performed on an “as needed” basis</td>
</tr>
<tr>
<td><strong>Systemic anti-inflammatory therapy added</strong></td>
<td>if unresponsive to topical therapy</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>Oral cyclosporin</td>
</tr>
<tr>
<td>Oral azathioprine</td>
<td>Oral Mycophenolate mofetil</td>
</tr>
<tr>
<td><strong>Antibacterial and antiviral therapy</strong></td>
<td><strong>(Off label use!)</strong></td>
</tr>
<tr>
<td><strong>Additional treatment options</strong></td>
<td>Oral antihistamins</td>
</tr>
<tr>
<td>Allergen specific immunotherapy</td>
<td>Psychosomatic counseling</td>
</tr>
</tbody>
</table>
and have limited its use to severely affected patients over the age of 18 years.

### 4.1.6 Experimental Approaches

**Mycophenolate mofetil (MMF)** is a purine biosynthesis inhibitor used as an immunosuppressant for the treatment of moderate to severe AD [33, 40]. Only few reports have addressed the use of this drug in AD but no controlled study has been published so far. The drug is generally well tolerated when given as short-term oral treatment with 2 g a day. After 5 weeks the dosage can be reduced to 1 g a day and continued for another 3 weeks. Occasional herpes retinitis has been recorded and should be taken care of.

**Immunotherapy** has been tried in old studies but no benefit could be shown in AD, leaving the role of this treatment open. These findings have also suggested over years that AD is a contra-indication of immunotherapy. More recently, new studies using specific immunotherapy in AD patients sensitized to D. pter. have led us to revise this classical notion [41]. Further studies are now ongoing to validate this concept [42]. Furthermore, a new area of study which is promising is the sublingual immunotherapy (SLIT) especially for children, but it awaits to be proved efficient in AD [43].

In the past years, advances in immunopharmacology and particularly biologicals have provided clinicians with new molecules developed to interfere with molecular mechanisms such as cytokine-receptor interactions and the resulting recombinant molecules represent a breakthrough in the management of chronic diseases. While patients suffering from severe psoriasis, another chronic inflammatory skin disease, have greatly benefited from biologicals, AD patients are still awaiting a similar gift. Only few reports about the use of such molecules are available but no clinical trials have been accomplished so far. It remains to be determined whether omalizumab, an anti-IgE monoclonal antibody, will provide a substantial progress in the management of severe forms of AD, although the high levels of circulating IgE in these patients probably hamper its use in this indication. So far only few reports have suggested that omalizumab may be of clinical benefit for AD patients [44] while others suggested that it is not the case (it should be mentioned that the negative reports included only 3 patients with very high IgE levels) [45]. Clearly, clinical trials according to modern standards are warranted [46].

Besides anti-IgE approach, the use of “anti-inflammatory biologicals” based on anti-TNF strategy (infliximab) or anti-CD11a (efalizumab) has been successfully tested in few case reports. Indeed, Efalizumab (anti-CD11a) has been introduced as a promising alternative to current immunosuppressive therapies [47], although further double-blind placebo-controlled studies are needed to test its efficacy and safety. Infliximab (anti-TNF-α) has also been reported to be successful in some reports [48]. However, one has to keep in mind that side effects of biologics may be serious and need further evaluation in placebo-controlled clinical trials.

### 4.1.7 Complications to Avoid

**Impetiginization** with *Staphylococcus aureus* is the most frequently observed complication of AD. We usually treat this impetiginization with a short course of oral cephalosporin, e.g., Cephadroxil 1 g b.i.d., for 10 days. Relapses can be prevented by compounding antiseptic substances such as triclosan into the daily emollient or by using silver-coated textiles [49, 50].

**Eczema herpeticum**, the widespread, disseminated infection of AD lesions with the herpes simplex virus, is still one of the few true emergencies in dermatology [51]. The diagnosis is suspected on clinical grounds if a monomorphic eruption of nonitchy, dome shaped blisters arises in an insufficiently treated AD patient. Eczema herpeticum may occur in every age group and is seen more frequently in severely affected patients with a high total serum IgE and an early onset of the underlying AD [52]. Eczema herpeticum is treated with systemic aciclovir for at least 7 days. The most effective intravenous administration is aciclovir 5–10 mg/kg body weight t.i.d., whereas aciclovir 400 mg tablets must be administered 5 times per day [51].

**Eczema molluscum** is the disseminated infection of AD with the molluscum contagiosum virus. It is more annoying than dangerous and can be treated in many different ways. Most approaches are based on a physical destruction of the lesion and subsequent activation of the immune system against the infected cells [51]. The number and location of the lesions, as well the patient’s age have influence on the optimal therapy.
Skin atrophy due to steroid overuse is an unnecessary complication of AD treatment and may be avoided by proper education of the patient.

Take Home Messages

- The overall goals in the management of AD are (1) the improvement of epidermal barrier function and (2) a better control of the clinical and subclinical inflammation. Mild and moderate cases of AD respond nicely to topical corticosteroids and topical calcineurin inhibitors. Systemic treatment with corticosteroids, calcineurin inhibitors, and other substances is rarely needed and indicated in severe cases only.
- After improvement of the skin lesions, a diagnostic program including a skin prick test should be scheduled. In addition, patch tests with a standard series including the most common emollients, emulsifiers, fragrances and drugs, as well as an atopy patch test including grass pollen, house dust mite and cat dander should be performed by an experienced dermatologist. Dietary restrictions should be recommended only in cases of clearly food allergic AD patients, as proven by skin tests and provocation tests in a diagnostic diet.

4.1.8 Global Variations

AD is a paradigmatic genetic complex disease where the genetic background as well as environmental factors plays a major role. Given the fact that genetic variations are not to be expected in an evolutionary limited period such as one or two hundred years, the impact of environmental factors which are subjected to significant changes in quite a short period of time have to be considered more stringently. Recent epidemiological studies have shown that cultural and economic backgrounds in concert with the hygiene hypothesis are of great importance for the worldwide increase in allergic diseases. How will AD evolve in this context is still unclear. Combining data from epidemiology, genetics, skin physiology and immunology, and allergy provides new areas of research which will certainly provide us new perspectives and new concepts in the pathophysiology and management of this disease as well as more insight in the putative causes of worldwide differences in the prevalence of this disease. The role of innate immunity which has been underestimated over years is now the subject of numerous projects and functional genomics will help us to better understand the consequences of so many genetic variants in candidate genes and could potentially deliver future prognostic tools for this disease, its prevention and therapeutic response.

References


Pruritus
Sonja Ständer and Thomas A. Luger

4.2

Key Features

▷ Pruritus can be directly evoked in the skin by chemical mediators.
▷ Pruritus can also be generated or modified in the CNS independently of peripheral stimulation.
▷ Chronic pruritus is based on same cutaneous neurobiology as acute itch, but central mechanisms are subjected to neuroplasticity resulting in sensitization toward itch.
▷ Clinical characteristics of pruritus allow only to a certain degree to conclude the underlying causes but may offer an algorithm for diagnosis.
▷ Administration of agonists or antagonists at cutaneous sensory neuroreceptors may inhibit of pruritus.
▷ Treatment of chronic pruritus demands development of new substances directly acting at neuronal structures in the skin or the CNS.

Abbreviations

AD    Atopic dermatitis
CB    Cannabinoid receptor
CGPR  Calcitonin gene-related peptide
CNS   Central nervous system
DRG   Dorsal root ganglia
fMRI  functional magnetic resonance imaging
NGF   Nerve growth factor
PAR-2 Proteinase-activated receptor-2
PEA   Palmitoylethanolamine
SP    Substance P
Trp   Transient receptor potential

4.2.1 Etiology and Pathophysiology

Pruritus is defined as an unpleasant cutaneous sensation leading to the desire to scratch. This physiological self-protective sensation guards the skin against harmful substances including parasites or plants. Pruritus can be directly evoked in the skin by mechanical and thermal stimuli or chemical mediators. In addition, it may also be generated or modified in the central nervous system independently of peripheral stimulation [1]. Pruritus is a major symptom of many skin diseases and various systemic diseases. Acute itch may occur along with e.g., urticaria or as a side-effect of drugs, e.g., chloroquin, which can easily be treated. More often a chronic, severe, generalized pruritus develops e.g., in cholestatic and renal diseases or in atopic dermatitis (AD). Chronic rubbing and scratching leads to secondary skin lesions such as excoriations, lichenification, prurigo, and scars along with the release of inflammatory mediators that potentially induce or aggravate pruritic sensations resulting in an...
itch-scratch-cycle [2]. Conventional therapies often fail to alleviate these types of chronic pruritus. However, the current progress in understanding the neurophysiology of pruritus has contributed to develop new antipruritic therapeutic strategies [3]. Chronic pruritus is based on same cutaneous neurobiology as acute itch but central mechanisms are subjected to neuroplasticity resulting in sensitization toward itch [4]. Accordingly, modern antipruritic therapies aim to interfere with both cutaneous as well as central mechanisms (Table 4.2.1).

4.2.2 Clinical Characteristics and Diagnosis

Pruritus is not a disease per se but a symptom of many disorders. Accordingly, intensity and quality of pruritus, clinical characteristics, and clinical presentation of patients may vary. Several diseases share same characteristics (e.g., mechanical-induced pruritus in urticaria, mastocytosis, cholestatic pruritus and hydroxyethyl starch-induced pruritus) or may result in same clinical presentation (e.g., prurigo in renal disease or AD). Thus, the clinical characteristics allow only to a certain degree to conclude the underlying causes but may offer an algorithm for diagnosis. Accordingly, a recently defined classification is oriented at the clinical presentation of the patients [5]. Three groups of patients have been defined (Fig. 4.2.1).

Pruritus on primarily noninflamed skin: patients who complain about a generalized or localized pruritus without initial occurrence of skin changes. Pruritus on primarily inflamed skin: an skin disease (dermatosis, cutaneous lymphoma, leukemic infiltrates, etc.) underlies pruritus. Chronic secondary scratch lesions ranging from simple linear or round erosions, excoriations, crusts to macular amyloidosis, lichen simplex, lichen amyloidosus, or prurigo nodularis have to be seen separately. These conditions which previously have been described as independent entities are regarded today as a secondary scratch-induced phenomenon, preceded by pruritus based on primarily inflamed or noninflamed skin.

4.2.3 General Therapeutic Outline

Considering the diversity of underlying causes in pruritus, standardized recommendations of antipruritic therapies do not exist. An individual therapeutical concept has to be developed for every patient considering age, pre-existing diseases and medications, severity of pruritus, impact on quality of life and underlying origin of pruritus [2]. In sum, prior to any further symptomatic therapy, a careful diagnostic evaluation and therapy of any underlying diseases are of priority. Some general principles can be recommended: First, the patient should be informed about general, pruritus-relieving measures. Creams/lotions, e.g., with menthol, camphor, urea, polidocanol or tannin can temporarily reduce pruritus and can be applied by the patient individually in case of night time pruritus [6]. Depending on the underlying cause, the scope of causal, antipruritic therapies ranges from the specific treatment of an underlying dermatosis, avoidance of a contact allergen, discontinuation of a medication, specific internal, neurological and psychiatric therapies up to the surgical therapy of an underlying tumor [2]. Pruritus often stops quickly when the underlying disease improves, e.g., during/after chemotherapy in Hodgkin’s disease. Next, a combined or consecutive, step-by-step, symptomatic, antipruritic treatment is necessary. Besides the use of antihistamines and short-term treatment with topical glucocorticosteroids, modern topical and systemic therapies have currently been developed based on new understanding of the neurobiology of pruritus [3].

4.2.4 Current Established Therapies and Neurobiological Basis

4.2.4.1 Targeting Pruritus Elicitation in the Skin

Itch, burning pain, noxious heat and cold as well as touch are generated in the papillary dermis and epidermis on free nerve endings of slow unmyelinated, so-called polymodal C-fibers (conduction velocity 0.5–2 m/s). Recent experimental studies demonstrated that many receptor systems are functionally expressed on sensory nerve fibers such as histamine receptors (H1, H3), proteinase activated receptor 2 (PAR-2), transient receptor potential vanilloid 1 (Trpv1), cannabinoid receptor 1 and 2 (CB1, CB2) and mu-opioid receptor (MOR) [1, 4]. All receptors contribute to cutaneous induction (H1, Trpv1, PAR-2) or inhibition of pruritus (CB, MOR) (Table 4.2.2, Figs. 4.2.2 and 4.2.3).

Dermal mast cells act in close interaction with nerve fibers and contain many substances which act as direct
### Table 4.2.1 Modern antipruritic therapies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Target</th>
<th>Effective in pruritus of (Diagnosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level of action: skin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Topic treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsaicin cream 0.025 –0.1%, 3–6 times daily</td>
<td>Vanilloid receptor subtype 1 (TrpV1)</td>
<td>Localized forms of pain and pruritus such as notalgia paresthetica, PUVA-itch and pain, postzosteric neuralgia, brachioradial pruritus, aquagenic pruritus, and prurigo nodularis</td>
</tr>
<tr>
<td>Palmidrol (PEA) containing cream, twice daily</td>
<td>Cannabinoid receptors (CB1, CB2)</td>
<td>Uremic pruritus, pruritus of unknown origin, lichen simplex, prurigo nodularis, localized pruritus</td>
</tr>
<tr>
<td>Calcineurininhibitors pimecrolimus 1%, tacrolimus 0.1%</td>
<td>TrpV1</td>
<td>Pruritus in atopic dermatitis, prurigo nodularis, chronic irritative hand dermatitis, rosacea, graft-vs-host-disease, lichen sclerosis; genitoanal pruritus, pruritus of unknown origin</td>
</tr>
<tr>
<td>Cold, menthol, icilin</td>
<td>TrpM8 (CMR1), ANKTM1</td>
<td>Reduction of pruritus of any kind for a short time</td>
</tr>
<tr>
<td>Anesthetics, e.g., Polidocanol</td>
<td>Suppress activity of voltage-dependent sodium channels</td>
<td>Reduction of pruritus of any kind for a short time</td>
</tr>
<tr>
<td><strong>Systemic treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H1-Antihistamines</td>
<td>H1 receptors</td>
<td>Urticaria, mastocytosis, urticarial drug-reaction, combination of antihistamines: atopic dermatitis, prurigo nodularis, pruritus of multifactorial origin in elderly patients</td>
</tr>
<tr>
<td>H1-Antihistamine Ketotifene</td>
<td>H1 receptors, mast cell stabilization?</td>
<td>Renal pruritus, urticaria</td>
</tr>
<tr>
<td>H2-Blocker Cimetidine</td>
<td>H2-receptors</td>
<td>Severe forms of neoplastic pruritus</td>
</tr>
<tr>
<td>Leukotrien receptor antagonist montelukast</td>
<td>Leukotrien D4 receptor</td>
<td>Atopic dermatitis, urticaria, urticaria factitia, aquagenic pruritus</td>
</tr>
<tr>
<td>Cyclosporin A</td>
<td>Suppression of IL-2</td>
<td>Atopic dermatitis, prurigo nodularis</td>
</tr>
<tr>
<td><strong>Level of action: Central nervous system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticonvulsants Gabapentin, Pregabalin</td>
<td>E.g., nerve membrane stabilization by blockade of calcium channels</td>
<td>Brachioradial pruritus, notalgia paresthetica, meralgia paresthetica, small fiber neuropathy, hydroxyethyl-starch (HES)-induced pruritus, renal pruritus, diabetogenic pruritus</td>
</tr>
<tr>
<td>Mu-opioid receptor antagonists: Naltrexone, Nalmefene, Naloxone</td>
<td>Mu-opioid receptor on spinal cord neurons</td>
<td>Cholestatic pruritus, chronic urticaria, atopic dermatitis, prurigo nodularis, pruritic mycosis fungoides, HES-induced pruritus</td>
</tr>
<tr>
<td>Antidepressant: Amitriptyline, Clomipramine, Doxepine, Mirtazapine</td>
<td>Interfere with the presynaptic re-uptake of neurotransmitters such as serotonin and noradrenaline</td>
<td>Prurigo nodularis and chronic pruritus of unknown origin</td>
</tr>
<tr>
<td>Antidepressant: Serotonin re-uptake inhibitor (SSRI) Paroxetine, Fluvoxamine</td>
<td>Interfere with the presynaptic re-uptake of serotonin</td>
<td>Prurigo nodularis and chronic pruritus of unknown origin</td>
</tr>
</tbody>
</table>
Table 4.2.2 Receptors and their role in cutaneous pruriception

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Ligand</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction of pruriception</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histamine receptors: H1, H3, H4</td>
<td>Histamine</td>
<td>Pruritus neurogenic inflammation; sensitized by bradykinine, prostaglandins</td>
</tr>
<tr>
<td>TrpV1</td>
<td>Noxious heat (&gt;42°C), protons, capsaicin, anandamide</td>
<td>Cold, heat, burning pain, burning pruritus, noxious heat, sensitized by NGF, galanin, bradykinin</td>
</tr>
<tr>
<td>TrpM8 (on Aδ-fibers)</td>
<td>Cold (8–28°C), menthol, icilin</td>
<td>Cold</td>
</tr>
<tr>
<td>TrpA1 (AnkTM1)</td>
<td>Noxious cold (&lt;17°C), wasabi, horseradish, mustard</td>
<td>Pain induced by cold, burning</td>
</tr>
<tr>
<td>PAR-2</td>
<td>Tryptase, trypsin</td>
<td>Pruritus, neurogenic inflammation</td>
</tr>
<tr>
<td><strong>Suppression of pruriception</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid receptors: Mu-, delta-receptor</td>
<td>Endorphins, enkephalins</td>
<td>Suppression of pain, pruritus and neurogenic inflammation</td>
</tr>
<tr>
<td>Cannabinoid receptors: CB1, CB2</td>
<td>Cannabinoids</td>
<td>Suppression of itch, pain and neurogenic inflammation, release of opioids</td>
</tr>
<tr>
<td>CB1: anandamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CB2: PEA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 4.2.1 Clinical classification of chronic pruritus

Fig. 4.2.2 Role of pruritogenic neuroreceptors
4.2 Pruritus

and indirect mediators of itch. Accordingly, administration of neuronal receptor agonists or antagonists topically or systemically, as well as mast cell mediating agents proved efficacy during the past years next to conventional therapies such as topical or systemical corticosteroids or UV-therapy.

4.2.4.1 The Vanilloid Capsaicin

The vanilloid receptor subtype 1 (VR1/Trp (Transient receptor potential) V1) is a nonselective heat-activated cation channel that is activated by vanilloids (e.g., capsaicin), the endogenous cannabinoid anandamide, increase of temperature within a noxious range (above 42°C), and by protons (pH below 5.9) [7, 8]. On sensory nerve fibers, vanilloid receptor activation leads to depolarisation and release of secretory granules containing neuropeptides such as SP or CGRP [9]. Repeated stimulation of the receptor, e.g., by application of capsaicin for several days induces desensitization of nerve fibers, inhibition of neuropeptide accumulation and suppression of painful and pruritic sensations. Capsaicin is therefore in use as a cream of 0.025–0.1% (3–6 times daily) in mostly localized forms of pain and pruritus such as notalgia paresthetica, PUVA-itch and pain, postzosteric neuralgia, brachioradial pruritus, aquagenic pruritus, and prurigo nodularis [10].

4.2.4.1.2 The Cannabinoid

The Cannabinoid

N-Palmitoylethanolamine (PEA)

Endogenous as well as synthetic cannabinoids are known for their psychotic and analgetic potency upon systemic administration. Recently, both cannabinoid receptors CB1 and CB2 were found to be present on cutaneous sensory nerve fibers [11]. Experimentally, the cannabinoid receptor agonist HU210 was shown to attenuate histamine-induced excitation of nerve fibers leading to reduced itch and axon reflex erythema [12, 13]. First pilot trials with a cream containing low concentration of N-Palmitoylethanolamine (PEA) could relieve pruritus due to hemodialysis [14] as well as localized pruritus, prurigo nodularis and lichen simplex [15]. These preliminary data show that topically applied cannabinoid agonists may represent a new antipruritic therapy. It may be speculated that a cream containing a higher concentration of PEA will lead to better response and broader indication area.

4.2.4.1.3 Cold, Menthol, Icilin

Cold, menthol and icilin activate two cold receptors, TRPM8 (CMR1) and ANKTM1 [16, 17] on a subset of nociceptive sensory neurons. It was demonstrated that cooling the skin by lowering the skin temperature
results in relief of experimentally induced itch [6]. A similar effect could be achieved by menthol although the skin temperature was not decreased leading to application of menthol creams (3–5%). However, both cold and menthol reduce acute and chronic pruritus for a short time of several minutes only. The clinical anti-pruritic efficacy of icilin undergoes current evaluation.

4.2.4.1.4 Calcineurin Inhibitors

The introduction of topical calcineurin inhibitors resulted in a significant improvement in the treatment of AD. In addition to anti-inflammatory effects, rapid amelioration of pruritus could be observed. Interestingly, current studies raised indirect evidence that next to capsaicin also calcineurininhibitors may bind to the TRPV1 on cutaneous nerve fibers [18, 19] explaining the burning and stinging itch at the beginning of topical therapy. In case reports, pruritic dermatoses such as chronic irritative hand dermatitis, rosacea, graft-vs-host-disease, and lichen sclerosus were also treated successfully with pimecrolimus and tacrolimus. In addition, patients with generalized and localized pruritus including genitonal pruritus and prurigo nodularis responded to tacrolimus and pimecrolimus [20]. Best results were obtained in genital pruritus after cessation of initial burning. Further controlled studies are necessary to confirm these results.

4.2.4.1.5 H1-Antihistamines

Antihistamines have been for a long period the only specific antipruritic therapy in dermatological and non-dermatological pruritus. Histamine is stored in mast cells and keratinocytes while H1 receptors are present on cutaneous sensory nerve fibers [21]. Furthermore, most of the known itch mediators are potent mast cell and thereby histamine liberators and may lead to the induction of pruritus. Next to antihistaminergic effect, antihistamines can modulate immunological mechanisms such as reducing mediator release and expression of adhesion molecules, regulating the release of cytokines, chemokines and consequently inflammatory cells recruitment [22]. For example, azelastine inhibits production of cutaneous pruritogetic mediators such as leukotrien B4 [23]; loratadin suppresses production of leukotrien B4 by neutrophils [24], and desloratadine inhibits release of several interleukins (IL-4, IL-6, IL-8 and IL-13) from basophils [25, 26]. Levocetirizin significantly inhibits resting eosinophils adhesion to rhVCAM-1at endothelial cells [27] and abolished histamine-dependent expression of epidermal proinflammatory molecules such as IFN-gamma in a dose-dependent manner [28]. Fexofenadine suppresses the expression of ICAM-1 on eosinophils and may induce eosinophil apoptosis [29]. In urticaria, mastocytosis and urticarial drug-reactions, H1-antihistamines exhibit a clear effect on the histamine-induced triple response of neurogenic inflammation (erythema, wheal and flare) by competitive binding to H1 receptors on nerve endings and vessels. In all other pruritic diseases, especially AD, lowdosages of H1-antihistamines do not prove efficacy. However, high-dosage of antihistamines shows significant antipruritic effect in chronic pruritus of diverse origin as well as in chronic urticaria. A combination of antihistamines e.g., azelastine, levocetirizin, and fexofenadine (twice daily, each) proved in our hand, significant antipruritic effect in patients with AD, prurigo nodularis and pruritus of multifactorial origin in elderly patients [3]. The first generation antihistamine ketotifen was reported to mediate antipruritic effects in renal pruritus and urticaria [30, 31]. However, controlled studies are pending as of yet. Interestingly, the affinity of the antihistamines can vary due to cutaneous pH changes possibly explaining variation of antipruritic efficacy in inflammatory skin diseases [32].

4.2.4.1.6 H2-Blockers

The H2-receptor blocker cimetidine, developed for treatment of gastrointestinal ulcers, was described to mediate [33] antipruritic effects. Case reports demonstrated influence on severe pruritus in patients with solid cancer in high-dosages of cimetidine (1 g/day: 200-200-200-400 mg) [34]. Ranitidine, another H2-Blocker, reduces wheals and itch in urticaria, most probably by binding to H2 receptors on endothelial cells.

4.2.4.1.7 Leukotrien Receptor Antagonists

So far, the role of leukotrienes in the pathogenesis of pruritus is speculative, although there is some evidence about their relevance. Intradermally injected leukotriene B4 is able to provoke scratching in mice [35].
Additionally, a correlation of nocturnal itch and high urinary leukotriene B4 levels was found suggesting that leukotrienes may contribute to severe pruritus at night in AD [36]. Leukotriene receptor antagonists such as zafirlukast, zileuton and montelukast block cysteinyl leukotriene receptors. Most commonly, montelukast, a leukotriene D4 receptor antagonist, is approved for in asthma. However, montelukast proved clinical efficacy in urticaria, and urticaria factitia [21, 37, 38]. In our hands, also patients with aquagenic pruritus experience improvement under montelukast treatment. Zafirlukast and zileuton have been demonstrated to suppress pruritus in AD patients [39–41].

4.2.4.1.8 Immunosuppressant Cyclosporin A

Several interleukins, i.e., IL-2, IL-4, and IL-6 are known to play a role in the elicitation of itch; only recently IL-31 was discovered to play a role in pruritus of AD [42]. Also IL-2 was claimed to be a potent inducer of pruritus because high doses of recombinant IL-2 applied for cancer therapy, frequently provoke redness and cutaneous itching [43]. In fact, IL-2 elicited itch upon experimental skin-prick testing [44] by activation of a subpopulation of cutaneous C-fibers which are chemosensitive to histamine, bradykinin, and capsaicin [45]. Bradykinin thereby seems to enhance the effect of IL-2-induced itching on sensory nerves [46]. Consequently, suppressing IL-2 produces significant antipruritic effect. Cyclosporin A (CyA), a cyclic polypeptide with potent immunosuppressive effects, has been reported to have an itch-relieving effect in various diseases including AD. In a randomized study, CyA was demonstrated to significantly reduce itch intensity [47]. After discontinuation of this therapy, pruritus recurred immediately suggesting that CyA represents a symptomatic and not causal therapy of pruritus. Moreover, CyA is effective in pruriginous AD as well as prurigo nodularis due to various origins.

4.2.4.2 Targeting Pruritus Elicitation in Central Nervous System

The sensation “itch” is transmitted by cutaneous unmyelinated C-fibers to extracutaneous peripheral nerves running via the dorsal root ganglion to the spinal cord. On spinal level, neurons of the spinothalamic tract projecting into the thalamus were found to be selectively excited by histamine and thus probably participate in the transmission of prurceptive information [48, 49]. PET and fMRI studies in humans could show activation of several brain areas including thalamus and the primary sensory cortex after cutaneous histamine application [50]. Recent studies could demonstrate that pruritus-transmitting spinal cord neurons run separate from pain neurons to the brain but may interact. For example, upon scratching and inducing a moderate pain sensation, pruritus transmission is inhibited. This observation led to the application of several centrally acting substances which proved efficacy in severe pruritus.

4.2.4.2.1 Anticonvulsants: Gabapentin and Pregabalin

Gabapentin is an anticonvulsive with additional analgetic properties. By direct action at the spinal cord it is speculated to hinder the transmission of nociceptive sensations to the brain and thereby also suppress pruritus. The exact mechanisms are still discussed but are possibly based on nerve membrane stabilization by blockade of calcium channels or inhibition of the synthesis of neurotransmitters. Gabapentin is recommended as the therapeutic agent of second choice after failure of other antipruritic substances e.g., in renal or diabetogenic pruritus [51, 52]. In forms of neuropathic pruritus such as brachioradial pruritus, notalgia paresthetica, meralgia paresthetica, small fiber neuropathy or HES-induced pruritus, it should be applied as the first-choice substance [53]. The new substance pregabalin displays similar effects upon use as analgetic agent with better side-effect profile. The substance is a GABA analog which selectively binds to the \( \alpha_{2-3} \delta \) subunit of neuronal voltage-gated calcium channels. Pregabalin thereby modulates the presynaptic release of excitatory neurotransmitters, such as glutamate and noradrenaline. Further, pregabalin reduces the substance P-related activation of glutamate receptors (AMPA receptors) on noradrenergic synapses, total transmitter release, and finally neuronal activity [54, 55]. As a result, neuronal hyperexcitability is reduced and thus explains the clinical efficacy of pregabalin. In accordance with our experiences, in comparison of both substances, gabapentin clearly has stronger antipruritic effects than pregabalin.
4.2.4.2.2 Mu-Opioid Receptor Antagonists: Naltrexone, Nalmefene, Naloxone

Opioid receptor antagonists were originally developed for treatment of heroin dependence and to reverse symptoms of postanesthetic depression, narcotic overdose, and opioid intoxication. Clinical and experimental observations have demonstrated that pruritus can be evoked or intensified by endogenous or exogenous opioids [56, 57]. Though at cutaneous level, opioid receptors have an inhibitory action on release of neuropeptides, the antipruritic effect can be explained also by its action in the CNS. Activation of spinal opioid receptors, mainly mu-opioid receptors, located on pain transmitting neurons induces analgesia often combined with pruritus. Reversing this effect by mu-opioid receptor antagonists thereby results in inhibition of pruritus. Accordingly, several studies could demonstrate that mu-opioid receptor antagonists such as naltrexone, nalmefene, and naloxone may significantly diminish pruritus. Placebo-controlled studies demonstrated efficacy of nalmefene in cholestatic pruritus, chronic urticaria, and AD [58–60]. Case reports and large uncontrolled studies showed considerable reduction of pruritus by naltrexone in prurigo nodularis, pruritic mycosis fungoides, and hydroxyethyl-starch induced pruritus [61]. However, high rate of initial side-effects as well as high therapy cost leads to second line application of opioid receptor antagonists in chronic pruritus.

4.2.4.2.3 Antidepressants

Antidepressants have direct influence on central pruritus perception by so far unknown mechanisms. It is speculated that they interfere in the neuronal re-uptake of neurotransmitters such as serotonin and noradrenaline and thereby reduce pruritus perception. Accordingly, tricyclic (e.g., amitriptyline, clomipramine, doxepin) and tetracyclic (e.g., mirtazapine) antidepressants were applied in chronic pruritus or prurigo nodularis [3]. Doxepin additionally has antihistaminergic effects and is therefore frequently preferred. Currently, modern preparations are available, which unfold a similar effect along with a better side effect profile. The selective serotonin re-uptake inhibitor paroxetine was reported in individual patients to have antipruritic effects in polycythemia vera, psychogenic pruritus, and paraneoplastic pruritus [62–64]. In an own study, 60% of the patients with prurigo nodularis and chronic pruritus of unknown origin experienced significant antipruritic effects upon treatment with paroxetine and fluvoxamine [82]. In particular, caution is required regarding the side-effects. In healthy patients, side-effects occur only rarely while in elderly patients with a history of heart diseases, life-threatening cardiac side-effects may occur. In addition, if yet untreated depressions are suspected, a consultation from a colleague with psychosomatic or psychiatric knowledge before using the antidepressant is reasonable. Interestingly, direct targeting of serotonin by serotonin antagonist such as ondansetron or granisetron did not show high antipruritic effects [65–67].

4.2.5 Experimental Approaches

The cutaneous and central neurobiology of pruritus is very complex and underlies a regulation of variable, stress-vulnerable mechanisms. Accordingly, the therapies and underlying mechanisms presented here are only a few parts of the complex network of interactions and possible treatment strategies. Other mediators induce a peripheral or central sensitization of nerve fibers contributing to chronification of pruritus. For example, neurtrophins and their receptors play an important role in cutaneous nerve development and reconstruction after injury. They are released by non-neuronal cells, and after binding to specific receptors on the peripheral nerve endings are transported along the axon on the cell bodies in the dorsal root ganglia where they regulate expression of a variety of proteins involved in neuronal growth and sensivity. Nerve growth factor (NGF) may lead to sensitization of peripheral neuroreceptors such as histamine and capsaicin (TRPV1) receptor [68]. It was also demonstrated that NGF is overexpressed in prurigo nodularis and AD, and NGF and its receptors were speculated to contribute to the neurohyperplasia of the disease [69, 70]. Accordingly, therapies addressing NGF could be an therapeutic option in prurigo nodularis or AD to hinder chronification of pruritus.

Only recently, the proteinases activated receptor 2 (PAR-2) was demonstrated on sensory nerve fibers and is activated by mast cell mediators such as tryptase [71]. Activation leads to induction of pruritus and neurogenic inflammation comparable to the effects induced upon histamine release from mast cells [72,
In AD, PAR-2 was enhanced on primary afferent nerve fibers in the lesional skin suggesting that this receptor is involved in pathophysiology of pruritus in AD [74]. Accordingly, PAR-2 antagonists should be effective in suppression of peripheral induced pruritus. To date, these substances are used only for experimental and not therapeutic purposes. Also other recently discovered substances inducing peripheral pruritus represent targets for new antipruritic therapies such as IL-31 or neuropeptides such as SP or CGPR. Especially in severe forms of chronic pruritus such as renal pruritus and aquagenic pruritus, new effective therapies are necessary since current modalities are not helpful at a long-term level.

4.2.6 Complications to Avoid

Many of the described therapies act in the central nervous system. They must therefore be applied with caution. For example, gabapentin and also naltrexone develop severe side-effect at the beginning of treatment such as dizziness. Patients have to be informed carefully and instructed to stay at home and not drive a car, e.g. In elderly patients, renal parameter have to be monitored in systemic treatments since most described substances may cause renal insufficiency.

Take Home Message

Treatment of chronic pruritus demands application of modern therapies acting directly at neuronal structures in the skin or the CNS. Most important is the discovery of the origin of pruritus and the early start of an effective therapy to prevent the sensitization of the nervous system and thereby, chronification of the symptom.

4.2.7 Global Variations

To date, because of the foundation of an international Society and international network of pruritus researchers, only few variation in pruritus treatments exist. A major differences exists for the therapy of pruritus with thalidomide.. The antipruritic efficacy of thalidomide (200–400 mg/day) in prurigo nodularis has been described in a case series [75–77]. Furthermore, thalidomide is discussed as an important therapy option in the treatment of pruritus/prurigo nodularis of HIV/AIDS, as it does not have immunosuppressive effects [78]. 50% of treated patients, however, developed peripheral neuropathy. Improvement of pruritus was reported in nephrogenic pruritus [79], chronic pruritus of different etiologies [80], and primary biliary cirrhosis [81]. The authors themselves have not used thalidomide in pruritic diseases. In their opinion, a thalidomide application for this purpose should not be considered because other therapy options are available for most forms of pruritus, and there is a great possibility of neurotoxic side-effects caused by thalidomide.

References

4.2 Pruritus


4.3.1 Etiology and Pathophysiology

Urticaria is a disease characterized by localized and transient edema in skin and/or mucosa, usually accompanied by redness and itching. These eruptions are accompanied by small to moderate degrees of inflammatory cell infiltrations, involving cells such as lymphocytes, eosinophils, and/or neutrophils around small venules. When these types of disorders emerge predominantly in deep mucosa, especially those of lips and eye lids, they are generally referred to as angioedema. These symptoms are caused by localized vasodilatation, enhanced vascular permeability, and the activation of sensory nerves in the lesion. All these reactions may be induced by the release of histamine from mast cells. However, there are a number of contradictions against histamine as a main player in the pathogenesis of urticaria, especially that of chronic idiopathic urticaria [1, 2]. For instance, more than 20% of patients with chronic idiopathic urticaria are totally resistant to antihistamines and individual wheals in chronic idiopathic urticaria often last more than 12 h, in contrast to those of most physical urticarias and those induced by a direct injection of histamine that last not more than an hour. With the exception of kinins that may play a major role in a certain type of angioedema, no other key molecules have been identified in the pathogenesis of urticaria [3].

The mechanisms of wheal formation by vasoactive substances, stimuli for mast cells to release histamine, and clinical causes for urticaria are described below.

4.3.1.1 Mechanisms of Wheal Formation

Wheals and accompanying redness (Fig. 4.3.1a) are caused by an increase of vascular permeability and...
vasodilatation due to histamine and probably other vasoactive substances derived from mast cells, as described above. Strong edema may develop into whitish rather than reddish wheals surrounded by flare (Fig. 4.3.1b). Alternatively, increased blood flow in the wheal area may result in a pale halo around the wheal, due to so called “steal” effect [1] (Fig. 4.3.1c).

4.3.1.2 Mechanisms of Mast Cell Degranulation

A number of substances or conditions have been identified to induce mast cell degranulation, thereby accepted as causes for the wheal formation observed in urticaria (Fig. 4.3.2).

4.3.1.2.1 Activation of FcεRI

The best investigated mechanism for mast cell activation is that in type I allergy, which is triggered by exogenous antigens via antigen-specific IgE bound on mast cells and basophils [2]. When antigens enter the body and reach skin mast cells, they cross-link antigen-specific IgE bound to the high affinity IgE receptor (FcεRI), resulting in the release of histamine and other mediators.

Skin mast cells and peripheral blood basophils may also be activated by autoantibodies against IgE and/or FcεRI, by cross-linking of FcεRI. Moreover, the presence of cell-bound IgE may even be inhibitory for the activation of FcεRI by autoantibodies against FcεRI [2].
The activation of FcεRI by these autoantibodies may require or be augmented by the activation of complement activated products, especially C5a [4, 5]. Such autoantibodies may be detected in 30–50% of patients with chronic idiopathic urticaria, who develop a wheal and flare reaction upon dermal injection [6].

4.3.1.2.2 Complement

The complement-activated products C3a and C5a (anaphylatoxins) display powerful biological activities that lead to a sequence of inflammatory events, including the activation of skin mast cells and basophils. Among mast cells, the receptor for C5a (C5aR) is predominantly expressed on MC\textsubscript{TC}, a type of human mast cells, which contains tryptase, chymase, carboxypeptidase, and cathepsin G in its granules and mainly resides in connective tissues, but not on the MC\textsubscript{T} type, which possesses only tryptase as the major component of its secretory granules and is mainly distributed in mucosal membranes [2, 7]. Since the major types of skin mast cells are MC\textsubscript{TC}, and MC\textsubscript{TC} are predominantly distributed in the skin, it is feasible that complement plays a critical role in the pathogenesis of urticaria, which predominantly involves the skin.

Another pathway of complement activation that may be involved in the pathogenesis of urticaria is the production of kinins, which increases vascular permeability, especially in angioedema. The impairment of C1esterase inhibitor (C1-INH) may readily cause the increase of kinins, such as C2-derived kinin (C2b), and bradykinin. A continuous administration of an oral angiotensin converting enzyme (ACE) inhibitor for the treatment of hypertension may also cause angioedema due to its inhibitory effect on kininase that metabolizes bradykinin [3].

Other peptides derived from complement have also been suggested to activate mast cells. However, the involvement of complement in the pathogenesis of urticaria, except for the augmentation of mast cell activation by the autoantibodies and kinin formation in C1-INH deficiency, is mostly considered speculative (Fig 4.3.3).

4.3.1.2.3 Neuropeptides

Neuropeptides, such as substance P and α-melanocyte-stimulating hormone (αMSH), induce degranulation of skin mast cells, in vitro [2, 8, 9]. In the skin, mast cells are located in the vicinity of blood vessels and peripheral nerve endings, which contain substance P [10]. However, neither mast cells in mucosal tissues nor basophils in peripheral circulation release histamine in response to these peptides. Therefore, it is feasible that substance P selectively activates dermal mast cells. However, no
direct evidence has yet been reported for neuropeptides to induce wheals in patients with urticaria. They may act directly on vascular endothelial cells to cause flare around wheal rather than via mast cells [11].

4.3.1.2.4 Osmolality

Radiographic contrast media may cause urticaria, due to the high osmolality. Peachell and Morcos have demonstrated that diatrizoat, a high osmolar ionic monomer could induced histamine release from basophils and mast cells [12]. Media containing iso-osmolar and nonionic dimers show no or only marginal effects of histamine release even at the same concentrations as high osmolar ionic media.

4.3.1.2.5 Others (Opioids and Proteases)

Opioids, such as codeine and morphine, induce histamine release from skin mast cells, both in vivo and in vitro, and may cause urticarial reactions when administered to certain individuals [13, 14]. This type of histamine release was initially reported to be inhibited in the presence of naloxane (an opioid receptor antagonist) in vitro. However, Blunk et al. have recently demonstrated with in vivo microdialysis that histamine release in skin by opioids is independent of their potency as opioid receptor agonists [14].

Protease-activated receptor (PAR) 2 is activated by cleavage of itself by serine proteases, such as trypsin, trypase, and/or their agonists. It is widely distributed in a variety of tissues, including keratinocytes, activated endothelial cells, sensory nerves, and mast cells in the skin, and induces histamine release from skin mast cells in vitro [15]. Therefore, it is feasible that mast cells may further be activated by tryptases released from mast cells themselves in the skin.

The role of endogenous proteases and opioids in the pathogenesis of urticaria is a subject for investigations in future.

4.3.1.3 Causes of Urticaria

A number of factors may be involved in each patient with urticaria, making it difficult to identify a particular one as a cause of urticaria. Moreover, in spite of increasing knowledge concerning molecules that act on/in skin mast cells, knowledge regarding the pathogenesis of urticaria remains rather fragmented. From a clinical point of view, it is practical to divide such factors into two groups; direct stimuli for wheal formation, and other urticaria aggravating factors [16].

4.3.1.3.1 Direct Stimuli for Wheal Formation

Wheals are induced by specific stimuli in some types of urticaria either by a mechanism of type I allergy, or nonallergic forms. Stimuli may be exogenous substances, such as food and drugs, and environmental substances, or physical conditions, such as mechanical shear forces, heat, sunlight, cold, water, physical pressure, and vibration (physical urticaria). Internal bodily changes, such as sweating and emotional excitation may also cause urticaria (cholinergic urticaria, adrenergic urticaria) (Table 4.3.1). Specific IgE may be involved not only in mast cell activation by exogenous antigens, but also in those by physical stimuli, in some patients.

4.3.1.3.2 Urticaria Aggravating Factors

It is widely recognized that infections, often by viruses, possibly by bacteria, including Helicobacter pylori and occasionally by other microorganisms may be associated with the pathogenesis and/or the aggravation of idiopathic urticaria [17, 18]. Psychological stress and fatigue are also factors that may cause and/or aggravate urticaria. Food additives, salicylic acid, histamine, and some other ingredients in foods may also be involved in a single or short-term aggravation of urticaria (Table 4.3.2). A common characteristic feature of these factors is incomplete reproducibility to induce urticaria and limited applicability for many patients with urticaria. Namely, only some of these factors may be associated with some occasions of a limited population of affected patients to various degrees. Therefore, it is important for the physicians to carefully evaluate the degrees of involvement of such factors for individual patients.
4.3 Urticaria

### 4.3.2 Clinical Characteristics and Diagnosis

A diagnosis of urticaria is made readily by transient and localized edema, usually accompanying redness and itching in skin and/or mucosa that disappear within a few hours or possibly a few days at the longest. It is not unusual for physicians to make a diagnosis based on anamneses without observing the eruption. Historically, a number of classifications of urticaria have been proposed in terms of disease periods, etiology, triggers, and/or pathophysiology.

Each classification has some advantages, but none of them can completely separate whole urticaria without overlapping with disease entities among urticaria subtypes [19]. Therefore, the classification of urticaria is a matter of discussion (see Sect. 4.3.9.1). In this chapter, I described characteristics of the major subtypes of urticaria based on classifications employed by recently published guidelines for the treatments of urticaria in Europe and Japan [16, 20–22]. The original classifications in each guideline are listed in Table 4.3.3.

---

**Table 4.3.1** Direct stimuli that may cause whealing in urticaria

<table>
<thead>
<tr>
<th>Stimuli</th>
<th>Type of urticaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigen</td>
<td>Allergic urticaria</td>
</tr>
<tr>
<td>Physical stimuli</td>
<td></td>
</tr>
<tr>
<td>Mechanical shear</td>
<td>Physical urticaria</td>
</tr>
<tr>
<td>Cold</td>
<td>Mechanical urticaria (Factitia)</td>
</tr>
<tr>
<td>Sunlight</td>
<td>Cold urticaria</td>
</tr>
<tr>
<td>Pressure</td>
<td>Solar urticaria</td>
</tr>
<tr>
<td>Heat</td>
<td>Delayed pressure urticaria</td>
</tr>
<tr>
<td>Vibration</td>
<td>Vibratory urticaria (vibratory angioedema)</td>
</tr>
<tr>
<td>Water</td>
<td>Aquagenic urticaria</td>
</tr>
<tr>
<td>Sweating (result of exercise, hot bath/shower, and/or emotional stimuli)</td>
<td>Cholinergic urticaria</td>
</tr>
<tr>
<td>Emotional excitation</td>
<td>Adrenergic urticaria, Cholinergic urticaria</td>
</tr>
<tr>
<td>Exercise</td>
<td>Exercise-induced anaphylaxis, Food-dependent exercise-induced anaphylaxis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>antigen</td>
<td>Allergic urticaria</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Anaphylactoid reactions (intolerance),</td>
</tr>
<tr>
<td>preservatives</td>
<td>Urticaria reactions to radio contrast media (due to high osmomolality and ionic strength),</td>
</tr>
<tr>
<td>antibiotics</td>
<td>Redman syndrome (due to vancomycin),</td>
</tr>
<tr>
<td>radiocontrast media</td>
<td>Angioedema,</td>
</tr>
<tr>
<td>vancomycin</td>
<td>Other unclassified urticaria reactions or aggravation of idiopathic urticaria</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td></td>
</tr>
<tr>
<td>others</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Foods</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>antigen</td>
<td>Allergic urticaria</td>
</tr>
<tr>
<td>preservatives</td>
<td>Anaphylactoid reactions (intolerance),</td>
</tr>
<tr>
<td>other food additives</td>
<td>Other unclassified urticaria reactions or aggravation of idiopathic urticaria</td>
</tr>
<tr>
<td>histamine</td>
<td></td>
</tr>
<tr>
<td>others</td>
<td></td>
</tr>
</tbody>
</table>

ACE angiotensin converting enzyme; NSAIDs nonsteroidal anti-inflammatory drugs
### 4.3.2.1 Idiopathic Urticarias (Ordinary Urticarias) (Acute and Chronic Urticarias)

Wheals and itching of this type of urticaria occur spontaneously daily or almost daily for days, weeks, months or years. Anaphylaxis may occur in very limited number of cases of acute urticaria. It may be aggravated by a variety of factors listed in Table 4.3.1 and 4.3.2, but no fundamental cause can be identified in most cases. Duration and size of individual wheals

<table>
<thead>
<tr>
<th>Table 4.3.2</th>
<th>Factors that may aggravate urticaria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections</strong></td>
<td></td>
</tr>
<tr>
<td>Viral infections</td>
<td></td>
</tr>
<tr>
<td>Chronic infections with <em>Helicobacter pylori</em></td>
<td></td>
</tr>
<tr>
<td>Other bacterial infections</td>
<td></td>
</tr>
<tr>
<td>Parasitic infections</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td>Psychological stress</td>
<td></td>
</tr>
<tr>
<td>Diurnal cycle (evening toward early morning)</td>
<td></td>
</tr>
<tr>
<td>Menstrual cycle (pre or during the period)</td>
<td></td>
</tr>
<tr>
<td>Drugs (see Table 4.3.1)</td>
<td></td>
</tr>
<tr>
<td>Foods (see Table 4.3.1)</td>
<td></td>
</tr>
<tr>
<td>Other inflammatory or immunological disorders</td>
<td>(e.g., thyroiditis, serum sickness, etc.)</td>
</tr>
</tbody>
</table>

### Table 4.3.3.1 Classification of urticaria in EAACI/GA²LEN/EDF guidelines (2005) [20]

<table>
<thead>
<tr>
<th>Group</th>
<th>Subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous urticaria</td>
<td>Acute urticaria</td>
</tr>
<tr>
<td></td>
<td>Chronic urticaria</td>
</tr>
<tr>
<td>Physical urticaria</td>
<td>Cold contact urticaria</td>
</tr>
<tr>
<td></td>
<td>Delayed pressure urticaria</td>
</tr>
<tr>
<td></td>
<td>Heat contact urticaria</td>
</tr>
<tr>
<td></td>
<td>Solar urticaria</td>
</tr>
<tr>
<td></td>
<td>Urticaria factitia/dermographic urticaria</td>
</tr>
<tr>
<td></td>
<td>Vibratory urticaria/angioedema</td>
</tr>
<tr>
<td>Other urticaria disorders</td>
<td>Aquagenic urticaria</td>
</tr>
<tr>
<td></td>
<td>Cholinergic urticaria</td>
</tr>
<tr>
<td></td>
<td>Contact urticaria</td>
</tr>
<tr>
<td></td>
<td>Exercise-induced anaphylaxis/urticaria</td>
</tr>
</tbody>
</table>

### Table 4.3.3.2 Classification of major type urticarias in JDA guidelines (2005) [16]

<table>
<thead>
<tr>
<th>Group</th>
<th>Subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Idiopathic urticaria</td>
<td></td>
</tr>
<tr>
<td>1. Acute urticaria</td>
<td></td>
</tr>
<tr>
<td>2. Chronic urticaria</td>
<td></td>
</tr>
<tr>
<td>II. Urticaria that may be induced by a particular stimuli or load</td>
<td></td>
</tr>
<tr>
<td>3. Allergic urticaria due to exogenous antigen (except for 4)</td>
<td></td>
</tr>
<tr>
<td>4. (Urticaria in) Food-dependent exercise-induced urticaria</td>
<td></td>
</tr>
<tr>
<td>5. Nonallergic urticaria due to exogenous substances (except for 6)</td>
<td></td>
</tr>
<tr>
<td>6. Urticaria due to intolerance</td>
<td></td>
</tr>
<tr>
<td>7. Physical urticaria</td>
<td></td>
</tr>
<tr>
<td>(1) Mechanical urticaria, (2) Cold urticaria,</td>
<td></td>
</tr>
<tr>
<td>(3) Solar urticaria, (4) Heat urticaria,</td>
<td></td>
</tr>
<tr>
<td>(5) Delayed pressure urticaria, (6) Aquagenic urticaria</td>
<td></td>
</tr>
<tr>
<td>8. Cholinergic urticaria</td>
<td></td>
</tr>
<tr>
<td>9. Contact urticaria</td>
<td></td>
</tr>
<tr>
<td>III. Special urticaria or urticaria-like disease</td>
<td></td>
</tr>
<tr>
<td>10. Angioedema</td>
<td></td>
</tr>
<tr>
<td>11. Urticarial vasculitis</td>
<td></td>
</tr>
<tr>
<td>12. Vibratory urticaria (Vibratory angioedema)</td>
<td></td>
</tr>
<tr>
<td>13. Darie’s sign in Urticaria pigmentosa</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4.3.3.3 Classification of chronic urticaria and angioedema in BSACI guidelines (2007) [21]

<table>
<thead>
<tr>
<th>Description</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic urticaria</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Physical urticaria</td>
<td>Dermatographism</td>
</tr>
<tr>
<td>(Dermatographism)</td>
<td>Cholinergic</td>
</tr>
<tr>
<td>Cold</td>
<td>Cold</td>
</tr>
<tr>
<td>Exercise</td>
<td>Exercise</td>
</tr>
<tr>
<td>Aquagenic</td>
<td>Aquagenic</td>
</tr>
<tr>
<td>Solar</td>
<td>Solar</td>
</tr>
<tr>
<td>Vibratory</td>
<td>Vibratory</td>
</tr>
<tr>
<td>Drug-induced urticaria</td>
<td>IgE-mediated allergic</td>
</tr>
<tr>
<td>Contact urticaria</td>
<td>IgE-mediated allergic</td>
</tr>
<tr>
<td>Angioedema without wheals</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Idiopathic C1 inhibitor deficiency (Hereditary angio-oedema)</td>
<td></td>
</tr>
<tr>
<td>Paraproteinemia (monoclonal paraprotein binding C1 inhibitor)</td>
<td></td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Urticarial vasculitis</td>
</tr>
<tr>
<td>Rare syndromes</td>
<td>Cryopyrin associated periodic syndrome (CAPS) Schnizler’s syndrome</td>
</tr>
</tbody>
</table>
4.3 Urticaria

Table 4.3.3.4 Clinical classification of the urticarias in BAD guidelines (2007) [22]

<table>
<thead>
<tr>
<th>Ordinary urticaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute (up to 6 weeks of continuous activity)</td>
</tr>
<tr>
<td>Chronic (6 weeks or more of continuous activity)</td>
</tr>
<tr>
<td>Episodic (acute intermittent or recurrent activity)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical urticaria (reproducibly induced by the same physical stimuli)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical</td>
</tr>
<tr>
<td>Delayed pressure urticaria</td>
</tr>
<tr>
<td>Symptomatic dermographism</td>
</tr>
<tr>
<td>Vibratory angio-oedema</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thermal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholinergic urticaria</td>
</tr>
<tr>
<td>Cold contact urticaria</td>
</tr>
</tbody>
</table>

| Localized heat urticaria      |
| Other                        |
| Aquagenic urticaria           |
| Solar urticaria               |
| Exercise-induced anaphylaxis  |

<table>
<thead>
<tr>
<th>Angio-oedema without wheals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
</tr>
<tr>
<td>Drug-induced</td>
</tr>
<tr>
<td>C1 esterase inhibitor deficiency</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Contact urticaria (contact with allergens or chemicals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urticaria vasculitis (defined by vasculitis on skin biopsy)</td>
</tr>
</tbody>
</table>

| Autoinflammatory syndromes    |
| Hereditary                   |
| Cryopyrin-associated periodic syndromes (CIAS1 mutations) |
| Acquired                     |
| Schnitzler syndrome          |

Tend to be long and large as compared to physical urticaria and cholinergic urticaria. The shape of the wheal is the most heterogeneous among urticarias. It may accompany other types of urticaria, such as mechanical urticaria and angioedema. Diagnosis is made essentially by anamneses without particular clinical examinations. Those with less than 6 weeks or 1 month disease history are classified as acute urticaria and those with more than those periods are classified as chronic urticaria. This type of urticaria is most common among patients with urticaria who visit medical institutes and many of them are sensitive to oral antihistamines. In 30–50% of chronic (idiopathic) urticaria, autoantibodies against IgE or FcεRI that cross-link FcεRI may be detected by autologous serum skin test (ASST) and/or histamine release test with sera of the patients (autoimmune urticaria), as described above (Sect. 4.3.2.2.1) [4–6]. The severity and periods of disease activities in this type of urticaria have been reported to be larger and longer than those without autoantibodies [23, 24]. Others, however, have argued against such differences [25, 26].

4.3.2.2 Physical Urticarias

Wheals are usually induced in minutes in the area where physical stimuli have been applied and disappeared shortly, mostly within 10 min or an hour, except for delayed pressure urticaria, which appears half to a few hours later from the time of pressure and may last for hours or a few days. The diagnosis is mainly made from careful history taking and, when necessary, physical challenge testing with suspected stimuli and appropriate clinical examinations. It is important to appreciate that different physical urticarias can occur concurrently in the same patient. Chronic “idiopathic” urticaria is often associated with mechanical urticaria.

4.3.2.2.1 Mechanical Urticaria (Symptomatic Dermographism)

This is the most common type among physical urticarias, but relatively rare in infants. Wheals are reproduced by gentle stroking or rubbing of the skin and last less than 30 min before fading. In some patients, spontaneous itch may precede the rubbing. Mucosa is not usually affected and there are no systemic symptoms, but pruritis of whole body surface may be troublesome. Clinically, the above mentioned provoking test is easy and may be useful to confirm the diagnosis and evaluate the severity [6].
4.3.2.2 Cold Urticaria

Wheals are rapidly provoked by skin exposure to cold fluids, cold solid surfaces, or cold air (wind). Systemic symptoms, including angioedema of the oropharynx, may occur and can be severe, especially when provoked by extensive body immersion, such as in seabathing. As well as mechanical urticaria and solar urticaria, the reactivity to cold can be passively transferred by the serum of affected patients [27]. The transferable factor has been variously attributed to IgE or IgM. Cryoglobulins and cold agglutinin can rarely be identified in the sera of these patients.

4.3.2.3 Solar Urticaria

This is a rather rare type of physical urticaria. Wheals are induced by the exposure to sun light. There are action spectra that provoke wheals for each patient [28]. Investigations with a spectrometer may reveal the presence of wheal suppressing spectra for a certain population of the patients [28]. However, such examinations are worth mostly for diagnosis rather than for treatment options.

4.3.2.4 Delayed Pressure Urticaria

As its name suggests, whealing occurs following a latent period of 0.5–4 h after an application of pressure perpendicular to the skin. Unlike mechanical urticaria, individual wheals last for hours and often beyond a day. Cases are reported mostly among Caucasian populations. Barlow et al. have reported that about 40% of patients with chronic “idiopathic” urticaria have accompanying delayed pressure urticaria [29]. On the other hand, the number of cases of this type of urticaria reported in Japan is very limited and the condition is often not even commonly recognized [30] (see Sect. 4.3.7.2). As for other physical urticarias, diagnosis can be made by careful history taking, but can be made more solid by a provocation test with a metal rod weight applied perpendicularly on the back or thigh [29].

4.3.2.5 Other Physical Urticarias

Aquagenic urticaria, vibratory angioedema (urticaria), and heat urticaria are rare type of urticaria, where wheals are induced by exposure of skin to water, vibration and heat, respectively. As with the other physical urticarias, no further investigations are needed beyond establishing the diagnosis by careful history taking and appropriate challenge tests.

4.3.2.3 Cholinergic Urticaria

The symptoms of cholinergic urticaria are induced by stimuli that cause sweating, such as exercise, a hot bath, and psychological excitation. They are characterized by widely spread pruritic monomorphic maculopapular lesions (Fig. 4.3.4). The lesions can be painful, rather than itchy, but may subside in 15–45 min if the patient rests, cools down or relaxes. It is common in children and young adults, and rare in the elderly. It may be accompanied by angioedema and systemic symptoms including wheezing and/or rarely anaphylactoid symptoms. The diagnosis may be established by appropriate challenge testing with exercise or a hot bath [31]. Skin testing with acetylcholine may produce wheal and flare reactions, but not in all patients [31]. There is no indication for further investigations.

Historically, cholinergic urticaria has been classified as a physical urticaria, but a recent consensus report and guidelines for urticaria classified this urticaria apart from physical urticaria [16, 21, 32].

4.3.2.4 Urticaria Induced by Exogenous Antigen via Allergic Mechanism

Urticaria is one of the major symptoms in type I allergy, or anaphylaxis. Antigens in foods, medications, plants, insects, and other environments may cause urticaria when they enter the body and bind to mast cells and/or
basophils. In patients with food-dependent exercise-induced anaphylaxis (FDEIA), symptoms are induced only when they exercise after taking food to which they are sensitized [33, 34]. In the guidelines published on behalf of the British Association of Dermatologists (BAD) Therapy Guidelines and Audit Subcommittee, type I allergy was listed as a possible cause for acute urticaria, but single reactions in response to particular drugs were excluded from urticaria, whereas others included them in urticaria [16, 20–22].

### 4.3.2.5 Urticaria Induced by Exogenous Substance via Nonallergic Mechanism

A number of factors, including those in drugs and foods, may cause wheals in certain individuals who are sensitive to them. They resemble type I allergy in that they develop urticaria symptoms promptly when delivered into the body or, in some cases, even when just attached to the skin (contact urticaria). However, the reactions are independent of IgE, and skin tests with susceptible factors do not show any reaction, except for the case of contact urticaria. Most of urticaria reactions induced by radiocontrast media are due to high osmolality [12] (see Sect. 4.3.1.2.4). Although a number of studies have suggested that the inhibition of cyclooxygenase activities by aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) are involved in the pathomechanism of bronchospastic reactions of asthmatic patients, the mechanism of urticaria and angioedema induced by these drugs is largely unknown [35]. Interestingly, populations of patients with aspirin-induced asthma are essentially different from those with urticaria and/or angioedema induced by aspirin and/or other NSAIDs [35]. Amines including histamine, artificial additives, and other unidentified factors in food may also cause immediate wheal reactions. It is noteworthy that urticaria and/or angioedema induced by such factors may not be reproducible in the same patients and may be involved as potential aggravating factors for other types of urticaria [33, 36].

### 4.3.2.6 Angioedema

Angioedema is characterized by asymmetrical, nonerythematous, localized, transient swelling of localized area of skin and/or mucosa, such as eye lids, lips, oropharyngolaryngeal tissue, and gastrointestinal wall. Angioedema may occur with or without superficially spread wheals and may resolve with anti-urticarial treatments. On the other hand, unlike most of other type urticaria, individual edema of angioedema may last for 2–3 days and is usually not itchy. However, angioedema is otherwise considered as a special type of urticaria in recent literature [37, 38]. The pathogenesis of angioedema can be divided into two categories. One is similar to that of other type of urticaria, and the other is due to the increase of kinins either by a dysfunction of C1 esterase inhibitor (C1-INH) or the inhibition of kininase (Fig. 4.3.3) [3]. The dysfunction of C1-INH is either hereditary or acquired. In patients with hereditary angioedema (HAE; OMIM no. 106100), the level of plasma C1q is normal whereas the activity of C1-INH is impaired either by point mutations or a whole defect of the corresponding gene [37–39]. Acquired defects of C1-INH may be caused by lymphoproliferative disorders, such as B cell lymphoma, with a decrease of C1q, or autoantibodies against C1-INH. The inhibition of ACE, which also cleaves and inactivates kinin may increase the level of bradykinin, as well [38].

### 4.3.2.7 Other Types of Urticaria

**Urticaria vasculitis** is a disease entity that resembles chronic idiopathic urticaria, but with histological evidence of vasculitis in involved skin. Individual wheals may be painful rather than itchy, last for 2–3 days, and disappear leaving pigmentation. They are often accompanied by fever, arthralgia, decrease of complement, and an increase in erythrocyte sedimentation rate. It may be associated with systemic lupus erythematosus (SLE) [40]. **Urticaria pigmentosa (cutaneous mastocytosis)** has been historically classified in urticaria. It may develop wheal in response to physical stimuli, especially mechanical rubbing (Darie’s sign), on pigmented plaque where mast cells accumulated (see Chap. 4.4).

### 4.3.2.8 Diagnosis

A diagnosis of urticaria is made, if there is a transient appearance of individual skin eruptions leaving no
trace, such as pigmentation or desquamation. It is easily confirmed by anamneses and/or inspection of the affected skin without further examinations. However, it is important to make a further precise diagnosis of the type of urticaria for adequate treatment of the patient. Idiopathic urticaria is diagnosed if spontaneous occurrence is confirmed by history and/or negative results of loading tests with suspected stimuli. The diagnosis of physical urticarias and urticaria pigmentosa can be substantiated by challenge tests with stimuli suspected by histories of patients.

The detection of antigen-specific IgE in blood and/or skin by solid phase immunoassays, leukocyte histamine release tests, and skin tests may be useful for the diagnosis of urticaria induced by exogenous antigens. However, such examinations are of no use for the other types of urticaria. Loading test with suspected food and exercise may be necessary for diagnosis of FDEIA [33, 34].

Levels of complement (C3, C4 and CH50) and C1-INH are useful for the diagnosis of angioedema due to C1-INH deficiency [38]. Skin biopsies may be useful or even essential for the diagnosis of urticaria pigmentosa (see Chap. 4.4) and urticarial vasculitis [40]. Otherwise, there is no common and established clinical examination to explore the cause of urticaria.

4.3.3 General Therapeutic Outline

The principle of treating urticaria is the removal of factors that cause, provoke and/or aggravate urticaria, and the use of pharmaceuticals, such as antihistamines as a mainstay, and other supplementary medications as needed. The aim and importance of each approach in the treatment are, however, variable among types of urticaria. In general, symptoms of idiopathic urticaria may be well controlled by drug therapies as compared with those of urticaria whose symptoms are induced by particular factors. Therefore, for patients with urticaria that is directly induced by a particular factor, such as drugs, food, or physical stimuli, identification and removal of such factors is more important than drug therapies. In limited cases of such patients, repeated exposure to the provoking stimuli may desensitize them for those stimuli. On the other hand, disease control by drug therapies is usually more important for patients with idiopathic urticaria. The content of drug therapies should be carefully decided based on the balance between risks and benefits.

In emergency cases, either hypovolemic shock due to anaphylaxis, or suffocation by laryngeal edema due to angioedema, first aid for life saving, such as adrenaline injection, rapid infusion, and/or airway establishment are essential. If the symptoms are not life threatening, but extremely severe upon presentation, rapid acting medications, such as intravenous or intramuscular injection of an antihistamine, and corticosteroids may be necessary. In attacks of hereditary angioedema, accompanied by suffocation, infusion of tranexamic acid and/or C1-INH should be indicated [37, 39].

4.3.4 Current Established Therapies

Treatments of urticaria should be designed based on both the severity/emergency of symptoms and the type of urticaria. Therefore, precise diagnosis and evaluation are essential. Current established therapies for subtypes of urticaria are as follows.

4.3.4.1 Idiopathic Urticaria

It is important to control disease activity through the suppression of daily symptoms by medications and complementary efforts to avoid possible aggravating factors (Table 4.3.2). The mainstay in the treatment for this type of urticaria is oral administration of non- or less-sedating second generation antihistamines. If a standard dose of such antihistamines is not sufficient, a change to another antihistamine, a combination with different antihistamines or the increase of the same drug might be beneficial [16, 20–22].
to antihistamines. It is known that a short course of corticosteroids, for a few days or weeks, may suppress the symptoms and reduce the duration of symptoms [41].

4.3.4.1.2 Chronic Urticaria

The entire pathogenesis of chronic urticaria cannot be explained by any single factor or mechanism. The presence of autoantibodies against IgE or FcεRI cannot account for diurnal periodicity of symptoms, which is often observed in this type of urticaria. On the other hand, they may be aggravated by factors listed in Table 4.3.2, such as fatigue, infections or drugs, to various degrees. Moreover, patients with chronic urticaria may be complicated with other types of urticaria, especially mechanical urticaria. Therefore, a full clinical assessment and explanations of such conditions to the patients in each case is important for the management of chronic urticaria.

In parallel with such efforts to assess disease conditions and removal of any identifiable aggravating factors, a continual administration of medication is necessary for most cases of chronic urticaria.

When any single or combined use of multiple antihistamines mentioned above fail to control symptoms, other drugs listed in Table 4.3.4 may be added to antihistamines. The optimal combinations and durations of the treatment may vary due to disease severity, periods of sickness, associations with other type of urticaria, etc. Evidences for those treatments are mostly provided in terms of the remission of the symptoms, rather than “cure” of the disease. It is, however, recommended to continue and gradually taper doses of the drug after symptoms have completely remitted [16, 21]. The usage of corticosteroids in the treatment of chronic urticaria is controversial. Although its effectiveness to suppress urticaria symptoms are well recognized, especially those in acute aggravations, prolonged use over weeks or months is generally not recommended, because of the adverse effects of long-term use [16, 20–22].

4.3.4.2 Urticaria with Symptoms Induced by Specific Factors

Antihistamines may alleviate symptoms of physical urticaria, cholinergic urticaria, and urticaria induced by exogenous antigens or particular factors, such as particular food, drugs, and environmental substances. However, in most cases, symptoms cannot be abolished as long as patients are exposed to causative factors. Therefore, for this type of urticaria, the identification and the removal or avoidance of the factor that induces symptoms are extremely important. In urticaria induced by a combination of multiple factors, such as FDEIA, the avoidance of either factor should be effective and enough to prevent the development of symptoms. For instance, patients with FDEIA induced by the combination of wheat and exercise can eat wheat-containing foods without symptoms as long as they do not take an exercise within a few hours of ingestion.

Corticosteroids may be effective to reduce symptoms that secondarily occur in anaphylaxis, but not useful for urticaria induced by antigens or those induced by specific factors mentioned above, except for the symptoms of delayed pressure urticaria [29]. The efficacy of leukotriene receptor antagonists on delayed pressure urticaria, cold urticaria, and aspirin-sensitive urticaria for limited numbers of patients has been reported [21]. Ciclosporin has also been reported to be effective for some cases of solar urticaria [42]. The other medications used for idiopathic urticaria are only of limited use for this type of urticaria [21].

Desensitization with antigens may be beneficial for patients with bee allergy, but using this approach with other antigens is still considered experimental or based on anecdotal case reports. Certain types of physical urticaria, such as solar urticaria, may subside by repetitive exposure to the stimuli (hardening). To treat symptoms of patients with cholinergic urticaria, whose sweating is impaired, sweat training may also be effective to reduce the sensitivity or even cure the urticaria.

4.3.4.3 Angioedema

The base line therapies for angioedema are same as those for other types of urticaria. Any identifiable factors should be removed as much as possible. It is noteworthy that there is duration, days, weeks, or even years, between initiations of the use of an ACE inhibitor and the aggravation or development of angioedema.
<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug name</th>
<th>Dosage range</th>
<th>EAACI recommendation</th>
<th>BSACI recommendation</th>
<th>BAD recommendation</th>
<th>JDA recommendation</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine H₂ receptor antagonist</td>
<td>Cimetidine, ranitidine, etc.</td>
<td>2 – 5 mg daily</td>
<td>2, D</td>
<td>C</td>
<td>II, C</td>
<td>(+)</td>
<td></td>
</tr>
<tr>
<td>Leukotriene receptor antagonist</td>
<td>Montelukast</td>
<td>10 mg daily</td>
<td>2, D</td>
<td>C (B for montelukast)</td>
<td>+</td>
<td>(++)</td>
<td></td>
</tr>
<tr>
<td>Tricyclic antidepressant</td>
<td>Doxepin</td>
<td>10–50 mg daily</td>
<td>2, D</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Not licensed in Japan</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>Nifedipine</td>
<td>15–60 mg daily</td>
<td>2, D</td>
<td>C</td>
<td>III, C</td>
<td>–</td>
<td>For patients who need antihypertensive treatment for vasospasm.</td>
</tr>
<tr>
<td>Chinese herb extracts (injection)</td>
<td>Monoammonium, glycyrrhizinate</td>
<td>5–20 mg daily</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>(++)</td>
<td>Limited use in Japan and Asian countries</td>
</tr>
<tr>
<td>Chinese herb extracts (oral)</td>
<td>Ju-mi-haidoku-to, etc.</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>(++)</td>
<td>Limited use in Japan and Asian countries</td>
</tr>
<tr>
<td>Anti leprous drug</td>
<td>Diaphenylsulfone, dapson</td>
<td>50–100 mg daily</td>
<td>3, D</td>
<td>–</td>
<td>+</td>
<td>(++)</td>
<td>For cases with angioedema or associated with angioedema</td>
</tr>
<tr>
<td>Antiplasmin drug</td>
<td>Tranexamic acid</td>
<td>750–2,000 mg daily</td>
<td>2, D</td>
<td>D</td>
<td>III, B (for angioedema without wheal)</td>
<td>(++)</td>
<td>For cases with angioedema or associated with angioedema</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>Prednisolone</td>
<td>5–40 mg daily (variable among guidelines)</td>
<td>4, D</td>
<td>D</td>
<td>Not recommended except in severe selected cases</td>
<td>(++)</td>
<td>Limited use for short and severe flare (days), and delayed pressure urticaria</td>
</tr>
<tr>
<td>Calcineurin inhibitor</td>
<td>Ciclosporin</td>
<td>4 mg/kg daily</td>
<td>2, C</td>
<td>B</td>
<td>I, A</td>
<td>(+++)</td>
<td></td>
</tr>
</tbody>
</table>

' The level of evidence and the strength of recommendation in five grades were designated in each guideline, from 1(I) to 4 (IV), and A to E(X), respectively, +, (+), (+++) recommended or mentioned for use, but the level of evidence and the strength of recommendation were not mentioned. – not mentioned as an option for treatments. (+) mentioned as a second-line treatment. (+++) mentioned as an experimental trial.

' Guideline as the result of a consensus reached during a panel discussion at the second International Consensus Meeting on Urticaria, Urticaria 2004, a joint initiative of the EAACI Dermatology Section and GA²LEN. This guideline was accepted by the European Dermatology Forum (EDF) and formally approved by the European Union of Medical Specialists (UEMS) (2005) [20]

' Guideline prepared by the Standards of Care Committee (SOCC) of the British Society for Allergy and Clinical Immunology (BSACI) (2007) [21]

' Guidelines prepared for dermatologist on behalf of the British Association of Dermatologists (2007) [22]

' Guidelines prepared by the Japanese Dermatologist Association (2005) [16]
It is important to prevent suffocation due to laryngeal edema. In case of a severe attack in HAE due to C1-INH insufficiency, airway establishment by intubation, drip infusion of tranexamic acid and/or C1-INH preparation is required. A kallikrein inhibitor and a bradykinin-2 receptor antagonist are under evaluation for clinical use and/or has been approved for the attack of HAE in Europe and North America.

For daily treatment of angioedema, oral administration of tranexamic acid may be effective as well as other pharmaceutical treatments for other types of urticaria [3, 37–39].

### 4.3.5 Experimental Approaches

#### 4.3.5.1 Idiopathic Urticaria

Immunotherapies for the most refractory and disabling cases of chronic urticaria were introduced with the recognition that some patients have circulating functional autoantibodies against IgE or FcεRI. Both urticaria activities and histamine-releasing activities in sera of patients were reduced or abolished by immunosuppressive or immunomodulative therapies, including plasmapheresis, intravenous immunoglobulin (IVIG), and oral ciclosporin [6]. However, more recent studies have suggested that ciclosporin [43] and other immunosuppressive therapies, including methotrexate [44], cyclophosphamide [45], tacrolimus [46], and mycophenolate [47] may also be effective for patients not necessarily having formal evidence of autoimmune urticaria.

#### 4.3.5.2 Urticaria in Cryopyrin-Associated Diseases

Urticaria or urticaria-like rash is a symptom of cryopyrin-associated periodic syndrome (CAPS), which consists of familial cold autoinflammatory syndrome (FCAS), Muckle-Well syndrome, and chronic infantile neurologic cutaneous and articular (CINCA) syndrome. All of them have recently been demonstrated as due to mutations in CIAS1, a gene coding cryopyrin, an intracellular protein, resulting in the increase of IL-1β. Anakinra, an IL-1 receptor antagonist, has been reported to be effective for such diseases [48, 49].

#### 4.3.5.3 Urticaria Mediated by IgE/FcεRI

The effect of anti-IgE monoclonal antibody, omalizumab on urticaria has first been recognized in the treatment of a patient with asthma complicated by cold idiopathic urticaria [50], followed by successful treatment of three patients with chronic idiopathic urticaria, in two of whom histamine-releasing autoantibodies (one for IgE, another for FcεRI) were detected [51]. More recently, the beneficial effect in a case of disabling cholinergic urticaria was also reported [52]. Since sensitivities of some, if not all, patients with urticaria for coldness or sweat have been shown to be mediated by specific IgE, it is feasible that a decrease of specific IgE and consequentially FcεRI by omalizumab may reduce such sensitivities. Thus, the effectiveness of omalizumab and/or other humanized monoclonal antibodies directed against IgE may be expected not only for patients with urticaria triggered by exogenous antigens via type I allergy, but also for certain population of patients with physical urticaria, cholinergic urticaria, and autoimmune urticaria mediated by specific IgE and/or FcεRI.

#### 4.3.6 Complications to Avoid

Urticaria itself is generally self-limiting and does not develop into other secondary diseases. However, when it accompanies other physical symptoms, complications of other disorders should be borne in mind.

The most serious disorder that may accompany urticaria is hypovolemic shock and suffocation due to anaphylactic shock and laryngeal angioedema. When wheals accompany purpura, and durations of individual wheals are not less than 24 h, they may be the symptoms of urticarial vasculitis, and suggest a potential risk of SLE. When arthralgia, continual fever elevation, and/or cold-hypersensitivity from infant are observed, Schnitzler’s syndrome and CAPS should be excluded. The incidence of H. pylori infection, malignant tumors, and other disorders of internal organs in
patients with urticaria is not statistically high, but treatments of such diseases may alleviate urticaria. Thyroid autoimmunity has been demonstrated to be associated with chronic urticaria, especially with those with anti-IgE or anti-FcεRI autoantibodies.

4.3.7 Global Variations

4.3.7.1 Classification

One of large variations among clinical classifications of urticaria is the definition of “chronic” urticaria. Most reports in European and North American literature employ 6 weeks [20–22], but those in Japanese generally employ 1 month as the minimum period of “chronic,” including the Guidelines for the Diagnosis and Treatment of Urticaria and Angioedema, published on behalf of the Japanese Dermatological Association (JDA) [16]. Another point of view is whether it includes all types of urticaria that occurs for the period, including those induced by physical stimuli, or limited to urticaria whose eruptions appear spontaneously [19]. The latter may also be called “chronic idiopathic urticaria.” This chapter employed the term, “idiopathic urticaria” for such type of urticaria, but some guidelines and literatures took “ordinary urticaria,” or “spontaneous urticaria,” as well (Table 4.3.3).

4.3.7.2 Clinical Characteristics

Elements of clinical symptoms observed in urticaria and angioedema are the same worldwide. However, the incidence of angioedema and delayed pressure urticaria, especially those complicated with other superficial type urticaria in Europe and North America appears to be much higher than those in Japan. The incidence of complication with angioedema in other urticaria was reported as 40–85% in Europe or North America [20], whereas only 19% of chronic idiopathic urticaria was complicated with angioedema in the author’s institute in Japan [30]. The incidence of hereditary angioedema identified in Japan is also small and may be sporadic. Delayed pressure urticaria, which complicated in as much as 37% of chronic idiopathic urticaria in UK [29] was very rare and observed only in 2% of chronic urticaria in Hiroshima, Japan [30].

The incidence of autoantibodies against IgE and FcεRI in Japan and Asian countries (up to 45%) [6, 53] may be somewhat less than that in Europe and North America (at least 30%) [21, 22]. Our recent study suggests that the incidence of anti-IgE type autoantibodies is dominant, whereas that of anti-FcεRI is dominant in Europe [6, 54].

4.3.7.3 Etiology

Peanut allergy is one of the major and severe manifestations in type I allergy in populations in Europe and North America, but not in Asian countries. It may though be on the increase in Japan. Hepatitis virus infections are a frequent cause for chronic urticaria in southern Europe, but a rare cause in northern Europe and Japan [16, 55]. Likewise, parasitic infections may be a cause of urticaria in developing countries, but rare in industrialized countries [55].

4.3.7.4 Therapies for Idiopathic Urticaria Nonresponsive to Single Doses of Antihistamines

All guidelines referred in this chapter suggested the increase of antihistamines beyond the doses of
manufacturers’ licensed recommendations. The guideline published by EAACI (the European Academy of Allergology and Clinical Immunology) and GA 2 LEN (the Global Allergy and Asthma European Network) [20] suggested an increase to as much as 4 times. However, the maximum dose of recommendation or allowance has not been generally established. The effectiveness of corticosteroids to suppress symptoms of idiopathic urticaria is widely recognized, but the way to use it may largely vary worldwide. Literature including guidelines from Europe and North American authors suggests short daily use of 50 mg prednisolone for 3 days or so with a course of tapering [22]. On the other hand, 5–15 mg prednisolone or its equivalent was mentioned as the third-line therapy for chronic idiopathic urticaria in Japan in the guidelines by JDA [16].

Oral administrations and/or injections of Chinese herb and the extract from rabbit skin (Neurotropin®) were licensed in Japan and mentioned as an option in the second-line therapy for chronic urticaria, but not in Europe and North America. On the other hand, the priority for ciclosporin in European guidelines was generally high although the levels of their recommendations are variable (grade A–C). It was mentioned only as an experimental option in the Japanese guidelines [16].

### References

4.4.1 Etiology and Pathophysiology

Mastocytosis is characterized by overproliferation and accumulation of clonal mast cells in peripheral tissues. Mastocytosis is a hyperplastic, rather than a neoplastic disorder which is frequently self-limited, especially in children. Except for the avoidance of mediator-releasing agents, the treatment strategy for mastocytosis is generally wait-and-see policy. Gain-of-function point mutations in the Kit protein are present in the majority of systemic patients, resulting in ligand-independent, constitutive activation of signaling to induce mast cell proliferation. Recent advances in our understanding of the molecular mechanism of systemic mastocytosis have led to the development of small-molecule compounds to target the disease-associated mutated Kit protein. Clinical trials are underway.

Key Features

- Mastocytosis is characterized by overproliferation and accumulation of clonal mast cells in peripheral tissues.
- Mastocytosis is a hyperplastic, rather than a neoplastic disorder which is frequently self-limited, especially in children.
- Except for the avoidance of mediator-releasing agents, the treatment strategy for mastocytosis is generally wait-and-see policy.
- Gain-of-function point mutations in the Kit protein are present in the majority of systemic patients, resulting in ligand-independent, constitutive activation of signaling to induce mast cell proliferation.
- Recent advances in our understanding of the molecular mechanism of systemic mastocytosis have led to the development of small-molecule compounds to target the disease-associated mutated Kit protein. Clinical trials are underway.

Mastocytosis is a range of heterogeneous disorders associated with abnormal regulation of MC development and proliferation, which consist essentially of normal-looking MCs [5, 6]. The clinical manifestations are directly related to tissue infiltration of MCs, which maintain their regular distribution, and to the release of chemical mediators by MCs resulting in skin rash, gastrointestinal symptoms, syncope, anaphylaxis, osteoporosis, organomegaly, and hematological disorders. Mastocytosis is rare in humans, affecting an estimated 1 in 1,000–8,000 dermatology patients, with an equal occurrence in men and women [7]. About 15% of mastocytosis cases are congenital, 30% of patients develop clinical manifestations before the age of 6 months, another 10% by the age of 2 years, and about
10% between 2 and 15 years of age. Therefore, most mastocytosis patients are children [8].

Most mastocytosis patients have no family history; yet more than 50 familial cases have been reported, with a dominant inheritance pattern in about one-third of these families (MIM 154800). Important advances have been made over the last decade in our understanding of the molecular pathogenesis of mastocytosis. Gain-of-function mutations in the Kit (CD117), a 145-kDa tyrosine kinase receptor for stem cell factor (SCF), are present in the majority of patients [9] (Fig. 4.4.1).

Kit-dependent cell types include hematopoietic stem cells, melanocytes, germ cells, and interstitial cells of Cajal. Therefore, Kit-SCF signaling is required for normal hematopoiesis, melanogenesis, gametogenesis, and regulation of gastric slow wave. Kit is also required for growth, differentiation, and functional activation of human MC [10, 11]. Crosslinking between one SCF and the extracellular immunoglobulin-like domains of two Kit molecules induces homodimerization of Kit and autophosphorylation at the Y568 and Y570 tyrosine residues of the juxtamembrane domain [12]. In case of canine MC tumors, which are one of the most frequent skin tumors in dogs and account for 16–21% of all cutaneous canine tumors, activating mutations consisting of internal tandem duplications have been identified in this juxtamembrane domain of Kit in 10–20% (Fig. 4.4.2) [13]. However, the exact mechanism underlying canine mast cell tumors without those somatic mutations has been unknown.

The mutations mapped to the tyrosine kinase domain of Kit, such as an aspartic acid-to-valine substitution at amino acid 816 (D816V), also result in ligand-independent constitutive activation of Kit signaling. This somatic mutation is identified in >80% of human patients with systemic mastocytosis [14, 15]. Although the D816V mutation is also recognized in pluripotential hematopoietic progenitors and is detectable in monocytes and B cells, the disease is restricted to MCs [16]. Probably D816V alone is not sufficient to exert cell proliferation. Therefore, secondary genetic lesions may be required to promote uncontrolled proliferation of MCs, especially in aggressive forms of systemic mastocytosis. Fip1-like 1/platelet-derived growth factor receptor α hybrid gene (FIP1L1-PDGFRα) carried in hypereosinophilic syndrome (HES) is one of the candidate genes [17, 18].

![Image](image_url)
4.4 Mastocytosis

4.4.2 Clinical Characteristics and Diagnosis

Because of the heterogenous clinical presentation and prognosis of mastocytosis, various classifications have been proposed. Table 4.4.1 shows the most widely accepted one, proposed by Hartmann and Henz [8], modified from that of Metcalfe [19] and Travis and his colleagues [20]. The clinical features of mastocytosis were first described by Nettleship and Tay in 1869, 8 years before Ehrlich discovered MCs.

**Table 4.4.1 Classification of mastocytosis**

<table>
<thead>
<tr>
<th>Indolent mastocytosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin only</td>
</tr>
<tr>
<td>Urticaria pigmentosa</td>
</tr>
<tr>
<td>Mastocytoma (solitary or multiple)</td>
</tr>
<tr>
<td>Diffuse cutaneous mastocytosis</td>
</tr>
<tr>
<td>Telangiectasia macularis eruptiva perstans</td>
</tr>
<tr>
<td>Systemic involvement</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mastocytosis with an associated hematological disorder (with or without cutaneous involvement)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloproliferative disorders</td>
</tr>
<tr>
<td>Myelodysplastic disorders</td>
</tr>
<tr>
<td>Aggressive mastocytosis (lymphadenopathic mastocytosis with eosinophilia)</td>
</tr>
<tr>
<td>Mast cell leukemia</td>
</tr>
</tbody>
</table>

4.4.2.1 Skin Manifestation

The skin is the organ which is most often involved; the most common eruption is a pigmented maculopapular or nodular lesion with a widespread symmetrical distribution. Sangster termed this disease, urticaria pigmentosa (Fig. 4.4.3).

Gentle rubbing of the lesion induces local wheals, erythema and often pruritus, termed Darier’s sign, due to local histamine release probably from mechanically activated MCs. Skin lesions occur mainly on the trunk and mucous membranes, and rarely on the face, head, palms and soles [21]. In the initial phase of the disease, the lesion density may increase over several years. Flushing occurs in about 50% of patients, and pruritus in 33–46% [22]. Blisters may develop, particularly in infants, but generally heal without scarring, except for rare erythrodermic cases (Fig. 4.4.4); however, residual hyperpigmentation may persist at the involved site.

Solitary or multiple nodules, termed mastocytomas, are also common in children with mastocytosis. Mastocytomas usually develop within the first 3 months of life and present as brown plaques, macules or nodules that can reach several centimeters in diameter. Blisters may be associated.

Diffuse cutaneous mastocytosis is a rare form of mastocytosis in which MCs infiltrate the entire skin. This condition generally arises within the first years of life and is often associated with systemic involvement. The skin may appear normal or may be thickened, with a reddish-brown or yellow color, i.e., typical peau d’orange [23]. Bullous eruptions are very common in this form. A rare erythrodermic form
of diffuse cutaneous mastocytosis presents as thickened, edematous skin, with a leather-like appearance (Fig. 4.4.4), [24]

Another uncommon form of mastocytosis namely telangiectasia macularis eruptiva perstans occurs mainly in adults [24]. The eruption consists of red, telangiectatic small macules with relatively little pigmentation. Darier’s sign is usually negative, and pruritus and blisters have not been observed so far. A few patients have also had systemic involvement, with MC infiltration of the bone marrow and persistent splenomegaly [25].

**4.4.2.2 Systemic Involvement**

Only 10% of patients with indolent mastocytosis experience extracutaneous symptoms. [26]. Children with urticaria pigmentosa generally have a good prognosis, with rare systemic involvement, and solitary mastocytomas usually resolve spontaneously in 2 or 3 years [27]. In contrast, adults with onset of extensive cutaneous lesions may develop systemic involvement. Clinical manifestations of systemic mastocytosis result from massive mediator release associated with MC accumulation in extracutaneous organs. Typical symptoms include nausea, vomiting, abdominal pain, diarrhea, palpitation, hypotension, vascular collapse, syncope, headache, dyspnoea and wheezing.

When examined carefully, however, even 30–50% of children as well as about 50–60% of adults with indolent cutaneous mastocytosis have bone marrow involvement [22]. Bone pain, osteoporosis, spontaneous fractures or fibrosis of the marrow may be associated. Extensive fibrosis of the bone marrow can lead to secondary hematological abnormalities such as anemia, thrombocytopenia, leukocytosis, leukopenia or sometimes eosinophilia [28]. Up to 30% of adult mastocytosis patients have been estimated to develop additional systemic hematological diseases such as a myeloproliferative or myelodysplastic syndrome, Hodgkin’s disease, HES or Castleman’s disease [29], whereas pediatric patients rarely develop hematological disorders [30].

In systemic mastocytosis, gastrointestinal involvement is also common [22]. Symptoms include nausea, vomiting, abdominal pain, cramps, malabsorption, peptic ulcers, diarrhea, esophagitis, esophageal strictures and gastrointestinal bleeding. Patients with more aggressive disease, sometimes associated with an accumulation of eosinophils, may suffer from hepatosplenomegaly and various degrees of fibrosis, portal hypertension, ascites and peripheral lymphadenopathy [31]. Neuropsychiatric abnormalities such as irritability, poor attention span, depression and impairment of short-term memory have also been observed.

Systemic mastocytosis may develop into an aggressive form, with severe symptoms including fever, hypotension, frequent episodes of flushing, fatigue and cachexia. These patients suffer more often from episodic flushing that can be provoked by changes of body temperature, exercise, emotional upset, infections or drugs such as opioid analgesics [7]. Whereas MCs are usually undetectable in peripheral blood, immature MCs have been reported in terminal leukemia patients. Paradoxically, at this point, cutaneous mastocytosis lesions may fade or even disappear [19]. Only a few cases of aggressive mastocytosis, also known as lymphadenopathic mastocytosis with eosinophilia, have been reported [7]. MC leukemia is an extremely rare disease
with atypical immature MCs that diffusely infiltrate the bone marrow and account for more than 10% of blood cells.

**4.4.2.3 Histopathology**

The diagnosis of mastocytosis is based on the characteristic clinical findings, history and physical examination. However, a skin biopsy is essential for confirmation of an increase in MCs (Fig. 4.4.5). Routine formalin fixation and toluidine blue stains (with the lower pH solution) are sufficient for diagnosis. The most selective surface marker phenotype for MCs is the co-expression of high levels of Kit and FcεRI. Tryptase is also a good marker selective for human MCs in immunohistochemistry [32]. Monoclonal antibody against chymase can identify the skin type of MCs but requires frozen sections [33].

In contrast to the various clinical types, the histopathological findings of mastocytosis are uniform; the common feature is the accumulation of an increased number of normal-looking MCs in the dermis. Generally, only a 4–5-fold increase in MCs in the dermis is observed in urticaria pigmentosa [24]. Infiltrates of spindle-shaped MCs are mainly located around blood vessels and skin appendages of the papillary dermis. In more confluent or nodular lesions, MCs infiltrate the entire dermis and occasionally even the subcutis. After mechanical stimulation, edema of the papillary dermis and subepidermal bullae may additionally be present. Eosinophils can accompany MC infiltrates. MC numbers are generally higher in lesional compared with nonlesional skin. Mastocytomas show marked, tumor-like aggregations of MCs throughout the dermis. In diffuse and erythodermic forms of mastocytosis, band-like infiltrates of MCs can be observed in the upper dermis. In contrast, histopathological changes of telangiectasia macularis eruptiva perstans usually demonstrate only scattered MCs around capillaries and venules of the superficial vascular plexus, associated with vascular dilatation.

**4.4.2.4 Blood Count and MC Mediators**

Blood count with peripheral smear can rule out associated hematological disorders such as anemia, leukopenia, leukocytosis or thrombocytopenia. A bone marrow biopsy should be performed in patients with abnormal findings.

Plasma histamine levels are elevated in the majority of mastocytosis patients. However, histamine released from MCs diffuses rapidly and is metabolized within minutes. In addition, the amount of histamine present in circulating basophils, if released, could raise plasma histamine levels about 500-fold and so great care must be exercised to avoid disrupting basophils when collecting blood. In contrast, serum tryptase levels, especially levels of α-protryptase, closely correlate with the course of mastocytosis and may therefore be used preferentially for the follow-up of patients with systemic mastocytosis [34, 35], because human MCs spontaneously and continuously secrete enzymatically inactive α-protryptase. Measurement of α-protryptase is even more sensitive than a bone marrow biopsy for determining systemic involvement.

**4.4.3 General Therapeutic Outline**

All patients with mastocytosis should be thoroughly informed about triggers that may lead to mediator release from MCs. They should also know about signs and symptoms indicating an anaphylactoid reaction. The most important triggers of systemic reactions are animal venoms, drugs (codeine, narcotic analgesics, polymyxin B, morphine, dextran, radiological contrast dyes, muscle relaxants, sympathomimetics), sudden
exposure to cold or heat, sun bathing, alcohol and mechanical irritation [8]. Allergens or agents to which patients have an individual intolerance (e.g., aspirin) should, of course, be avoided. In view of the risk of anaphylaxis, mastocytosis patients, especially those with a history of anaphylaxis, regularly carry a set of emergency medicines with them (antihistamines, corticosteroids and adrenaline).

Except for the avoidance of mediator-releasing agents, the treatment of mastocytosis is generally only symptomatic and will not change the natural course of the disease [36]. Patients with indolent mastocytosis usually have a favorable prognosis; systemic symptoms, the extent of systemic involvement, the MC burden, histological features or age at onset have not been correlated with a deleterious impact. Symptoms resolve spontaneously by adolescence in about 50% of pediatric patients [30]. Practically, solitary mastocytomas usually diminish within 2 or 3 years. Therefore, the treatment strategy for indolent mastocytosis is generally wait-and-see policy.

Childhood-onset lesions may persist in adulthood. Most adult patients have a chronic course of the disease, but spontaneous resolution is still possible [37]. Again, malignant mastocytosis is exceptionally rare. Nevertheless, potentially life-threatening complications such as anaphylaxis, cardiovascular collapse, hemorrhage and perforating peptic ulcers can arise in indolent mastocytosis on massive MC mediator release.

4.4.4 Current Established Therapies

4.4.4.1 Antihistamines

H1 antihistamines can relieve pruritus, flushing, wealing, malaise, abdominal pain, and bullae. H2 antihistamines are used to treat gastrointestinal symptoms. Patients with repeated anaphylactoid reactions should take H1 and H2 antihistamines on a regular basis.

4.4.4.2 Cromolyn Sodium and Anti-Inflammatory Agents

Gastrointestinal symptoms such as abdominal pain, nausea, and diarrhea also respond well to cromolyn sodium. Due to the low absorption rate of cromolyn sodium, it has no effect on systemic symptoms, including flushing, urticaria, and bone pain [38]. Aspirin and other nonsteroidal anti-inflammatory agents improve prostaglandin-dependent flushing in some patients who are not intolerant.

4.4.4.3 Ultraviolet Irradiation

Oral psoralen plus UVA (PUVA) and UVA1 irradiation effectively reduce the number of MCs as well as MC-derived mediator levels in the skin [39]. Usually, lesions gradually fade due to general tanning, and pruritus and other symptoms improve. However, symptoms almost invariably recur within several weeks in adults [39], and therefore, the benefits of UV irradiation should be carefully weighed against the potential adverse effects induced by prolonged irradiation.

4.4.4.4 Treatment of Mastocytomas and Bullae

Mastocytomas that cause systemic symptoms or mechanical problems can be treated with potent topical steroids under occlusive dressings. Repeated application of steroids may, however, cause cutaneous atrophy. Surgical excision of mastocytomas should be considered only as a last option, considering the natural history of most mastocytomas. In addition, surgical procedures and anesthetic management in mastocytosis patients are associated with a high risk of anaphylaxis. Bullae should be treated locally like burn blisters. Intravenous corticosteroids in combination with antihistamines have been successfully used in rare cases with severe bullous reactions [27].

4.4.4.5 Immunomodulatory Agents and Chemotherapy

Therapy for aggressive forms of systemic mastocytosis has been based on cytoreductive agents, mainly interferon (IFN) [40–42] and a purine analog, cladribine [42, 43], with the addition of steroids in some cases. However, responses are transient and occur only in a
subset of patients. In addition, IFN itself may induce dose-limiting adverse effects such as anaphylactoid reactions, hypothyroidism, thrombocytopenia and depression. We reported a patient with aggressive systemic mastocytosis who responded well to cyclosporin combined with low-dose methylprednisolone [44].

Patients with MC leukemia traditionally have been treated with chemotherapy regimens similar to treatments for acute myeloid leukemia [45]. Although these modalities can render significant MC reduction and symptom control in some patients, responses are transient, and the prognosis remains unchanged [46, 47]. Bone marrow transplantation is helpful to treat the hematological disorder in patients with mastocytosis, but fails to ameliorate the associated MC increase. Some patients with mastocytosis may also show prolonged survival after splenectomy [36].

4.4.5 Experimental Approaches

Recent advances in our understanding of the molecular mechanism of systemic mastocytosis have led to the development of small-molecule compound targeting disease-associated mutated Kit. Some of these promising agents are currently in clinical trials [48].

4.4.5.1 Imatinib Mesylate

Imatinib is a potent, competitive inhibitor of various protein tyrosine kinases, including Bcr-Abl, [49] PDGFR, [50] and Kit. Imatinib has demonstrated a significant suppressive effect against the wild-type and V560G mutant at the juxtamembrane domain of Kit, but failed to inhibit D816V at the tyrosine kinase domain [51]. Today imatinib shows sustained objective clinical responses in more than 50% of patients with gastrointestinal stromal tumor (GIST) – a tumor derived from Cajal cells bearing the juxtmembrane mutation V560G [52, 53]. In mastocytosis, imatinib is highly sensitive to the canine MC tumor carrying the juxtmembrane mutation [54], but the kinase activation loop mutant D816V, frequently encountered in human systemic mastocytosis, hampers the binding ability of imatinib. Thus, imatinib failed to inhibit the growth of malignant MCs from patients. On the other hand, eosinophilia is one of the indicators associated with poor prognosis in mastocytosis, but up to 50% of the patients with bone marrow and/or peripheral blood eosinophilia carry the imatinib-sensitive FIP1L1-PDGFRα, leading to the constitutive activation of the PDGFR kinase [55]. For this subset of patients, imatinib must be considered as first-line therapy [18, 56].

4.4.5.2 AMN107

AMN107 is a phenylamino-pyrimidine that is 20–30-fold more potent than imatinib against Bcr-Abl, with similar activity against Kit and PDGFR. The effect of AMN107 was examined on Ba/F3 cells transformed with murine Kit D814V, which is homologous to human D816V [57]. Unlike imatinib, AMN-107 effectively inhibited the growth of this cell line and induced cell death. Similar results were obtained when transformed with human D816V. AMN107 strongly decreased Kit phosphorylation in HMC-1.1 cells (which express V560G) but showed only weak effects on HMC-1.2 cells (which express V560G and D816V) [58].

4.4.5.3 Dasatinib

Dasatinib (BMS-354825) is a dual Src/Abl kinase inhibitor that is 300-fold more potent against Bcr-Abl than imatinib [59]. Dasatinib inhibited the kinase activity of wild-type Kit 20-fold more efficiently than imatinib, and, in contrast to imatinib, D816V was also inhibited with efficiency comparable to that for the inhibition of wild-type Kit. Dasatinib showed preferential cytotoxicity against neoplastic MCs in bone marrow mononuclear cell cultures established from patients with systemic mastocytosis [60].

4.4.5.4 PKC412

PKC412, an N-benzoyl-staurosporine, is a potent inhibitor against protein kinase C, vascular endothelial growth factor receptor 2 (VEGFR-2), PDGFR, FMS-like tyrosine kinase 3 (FLT3), kinase insert domain receptor (KDR) and Kit. PKC412 inhibits the growth of Ba/F3 cells transfected with D816V [61, 62]. A recent report shows that PKC412 is the first inhibitor which is able to suppress with equal efficacy, the
growth of human MCs bearing Kit mutations either in the kinase domain or in the juxtamembrane domain. PKC412 was administered to one patient with MC leukemia associated myelodysplastic syndrome/myeloproliferative disorder and bore D816V, resulting in significant reductions in the peripheral blood MC number and serum histamine level and a significant improvement in liver function tests [61]. However, the patient died after 3 months of therapy. In contrast to peripheral blood, there was minimal MC reduction in the bone marrow of this patient. However, PKC412 cooperated with AMN107 against both HMC-1 subclones, suggesting alternative therapeutic options in the event of emergence of PKC412 resistance [58].

### 4.4.5.5 Other Small-Molecule Kit Tyrosine Kinase Inhibitors [48]

The following are now under investigation: a heterocyclic anthranilamide analog, OSI-930; MLN518, initially designed as an FLT3 inhibitor; PD180970, a pyrido[2,3-d]pyrimidine inhibitor of Abl, Src, and Kit, and its derivative PD173955; the adenosine triphosphate (ATP)-based 2,6,9-trisubstituted purine analog AP23464 and a related compound, AP23848; the multitargeted tyrosine kinase inhibitor, SU11652, SU11654, and SU11655; another class of Kit inhibitors includes quinoxaline derivatives such as AGL2043 and the more recently reported EXEL-0862 [63].

### 4.4.5.6 Other Signaling Inhibitors

Among other functions, nuclear factor (NF-)κB modulates cell proliferation by upregulating the transcription of D-type cyclins. Exposure to exogenous stimuli, such as inflammatory cytokines, triggers the degradation of its inhibitor (IκB) by activating IκB kinase (IKK)-α and IKK-β, which induce IκB phosphorylation, ubiquitination, and proteolysis by the 26S proteasome. Spontaneous activation of NF-κB has been demonstrated in HMC-1.2 cells [64]. We recently reported that NF-κB activation as well as cell proliferation in both juxtamembrane and kinase domain of Kit mutants were inhibited by a selective IKK-β inhibitor IMD-0354, which also led to the suppression of cyclin D3 expression [64]. Interestingly, the drug inhibited NF-κB activation but not cell proliferation in normal human MCs, suggesting a limited degree of selectivity. These data suggest that cell cycle progression in neoplastic MCs may be highly dependent on NF-κB and cyclin D3. Hence, IκB kinase provides yet another target for the development of drugs against Kit-driven malignancies. Bortezomib appears to be efficacious in multiple myeloma through the inhibition of NF-κB activation [65], and its efficacy in systemic mastocytosis is currently under investigation in a clinical trial.

Kit activates the serine/threonine kinase mammalian target of rapamycin (mTOR), which regulates cell growth and cell cycle progression in MCs and is located downstream of phosphatidylinositol-3 kinase (PI3K)/Akt [66]. The mTOR inhibitor rapamycin induced marked cell growth inhibition of HMC-1.2 cells that harbored D816V but not cells that harbored V560G, thus showing an opposite inhibitory pattern in relation to imatinib [67]. It is noteworthy that this effect was observed at clinically achievable rapamycin doses (5 nM) in freshly isolated MCs from the patients who bore the D816V. These data provide validation for the clinical testing of rapamycin and its analogs in patients with systemic mastocytosis.

### 4.4.6 Complications to Avoid

Generally, the majority of mastocytosis cases are hyperplastic rather than neoplastic disorders, which are frequently self-limited, especially in children. Therefore, the principle rule for treatment is wait-and-see policy, except for the avoidance of mediator-releasing agents.

#### Take Home Message

The results for patients with systemic mastocytosis and their physicians are encouraging due to the unprecedented development of novel therapies for this disease. However, as we have learned from imatinib therapy in chronic myeloid leukemia, remissions induced by kinase-targeting therapy may not result in permanent disease control in all patients because of the development of drug resistance. Therefore, therapy with tyrosine kinase inhibitors alone may not be sufficient to cure mastocytosis.
4.4 Mastocytosis

4.4.7 Global Variations

Since the nature of mastocytosis does not vary globally, the therapeutic strategies do not differ.

References

Part V

Allergic Reactions and Hypersensitive Diseases
5.1.1 Etiology and Pathophysiology

It is important to differentiate between contact allergy and allergic contact dermatitis (ACD). A patient having acquired a contact allergy has met an allergen in a certain concentration (dose/cm²) that has given rise to a sensitization. ACD develops when the skin is re-exposed to sufficient concentration, (dose/cm²) of the allergen, i.e., it is the elicitation that gives rise to ACD.

ACD depends primarily on the activation of allergen-specific T-cells [7, 8], but humoral antibody-mediated reactions may also play a role [9].

5.1.2 Immunology

In this text, only a general simplified immunology will be discussed to enhance the clinical understanding of ACD.

The primary goal in preventing ACD is to prevent further damage by removing/avoiding the offending allergen.

5.1.2.1 Sensitization

This phase can be further divided into five steps [9]:

1. The allergen is bound to skin components: after penetrating the skin, the allergen is taken up by the main antigen-presenting cell in the epidermis, the Langerhans cell.
2. Activation of antigen-presenting cells: The allergen directly activates Langerhans cells and keratinocytes leading to cytokine release. The
activated Langerhans cells migrate and reach the lymph nodes.

3. Recognition: The naive T-cells in the regional lymph nodes meet the often processed allergen and activation takes place.

4. Proliferation of specific T-cells: After the activation by the antigen-presenting cell, the T-cells release cytokines and proliferate.

5. Systemic propagation of the specific T-cell clone: The T-cells enter the efferent lymphatics and recirculate from there.

The sensitization phase requires 7 days to several weeks.

### 5.1.2.2 Elicitation

The effector phase of ACD [9]. With renewed allergen contact, the elicitation starts. The reaction depends on the specific T-cells, their migratory capacities, the activation threshold, and the proinflammatory capacity of the allergen. The allergen will enter the skin as previously described, leading to cytokine release due to proinflammatory capacity, activation of allergen-specific T-cells, and massive cytokine release. The local cytokine and chemokine release will attract more T-cells and an eczematous reaction will develop.

The maximum is usually reached within 18–48 h.

### 5.1.3 Pathology

The ACD diagnosis is a clinical one based on the presence of a contact allergy diagnosed by epicutaneous testing. Biopsies are rarely necessary. Histology can sometimes be helpful in excluding other possible diagnoses.

### 5.1.4 Contact Allergens

What substances have the capacity to be contact allergens?

There are several prerequisites for a substance to become an allergen (Table 5.1.1).

Many contact allergens are weak allergens that require repeated exposure before they actually cause sensitization but there are also strong allergens that may sensitize after only one exposure [10]. Contact allergy to a weaker allergen may anyhow be more frequent in the society due to a larger exposure, as is the case with nickel.

A molecule that is in itself not sensitizing can be changed due to the environment through, for example, light, oxygen or heat, and thereby nonsensitizers can be transformed by chemical modification during storage and handling to become sensitizers. These molecules are often called prehaptenst [11]. When considering substances and their sensitizing potential, one must also consider what happens in the skin. A molecule, in itself nonsensitizing, can through enzymatic processes in the skin form sensitizers. These molecules are often called prehaptenst.

Also cross reactivity is important when contact allergens are considered. Cross reactivity is the ability of an activated T-cell to react with or bind an allergen that did not stimulate its production; i.e., two substances are so similar in their chemical structure that the T-cells do not discriminate but are triggered by both substances.

### 5.1.5 Skin Prerequisites

As explained, many factors may influence the development of ACD (Table 5.1.1), apart from the dose/cm², the sensitivity of the patient is of great importance.

<table>
<thead>
<tr>
<th>Table 5.1.1</th>
<th>Factors of importance in order for a substance to be a possible allergen.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Penetration through stratum corneum</strong></td>
<td></td>
</tr>
<tr>
<td>Size &lt;1,000 Da, usually &lt;500 Da</td>
<td></td>
</tr>
<tr>
<td>Sufficient number of molecules, i.e., the dose/cm², is of great importance for sensitization and also elicitation; the dose is not the same</td>
<td></td>
</tr>
<tr>
<td>Metals have to be in ionic form and for other molecules they have to be more or less lipophilic</td>
<td></td>
</tr>
<tr>
<td><strong>In the epidermis</strong></td>
<td></td>
</tr>
<tr>
<td>The small molecules must conjugate with proteins to enable sensitization or elicitation</td>
<td></td>
</tr>
<tr>
<td>The tertiary structure: there must be sufficient amount of antigenic determinants</td>
<td></td>
</tr>
<tr>
<td>The three dimensional structure is very important, only one of two isomers may be sensitizing, this phenomena is called enantiospecificity</td>
<td></td>
</tr>
</tbody>
</table>
5.1 Allergic Contact Dermatitis

Differences in exposure pattern and genetics may influence this.

There is a gender difference in the frequency of contact allergy to many allergens. For many allergens though, a large part of the explanation is due to differences in exposure patterns [13]. Age is another factor that influences exposure [14] to a great extent.

The ability of allergens to penetrate is also dependent on regional variation. Sensitization is increased in damaged skin. Skin exposed to irritants, as for example, the hands, often has injuries to the stratum corneum and thus sensitization may occur more easily. Occlusion promotes penetration and may contribute to sensitization. There are other factors that influence the tendency of sensitization: atopy downregulates Type 1 T-cells and subsequently most studies find a decreased tendency to sensitization [15–18], diseases such as lymphoma and psoriasis, medication [19], and exposure to UV-light also influence the patch test reaction [20–22].

5.1.6 Clinical Characteristics and Diagnosis

When defining ACD one must consider that the clinical picture is impossible to differentiate from contact dermatitis based on other etiologies.

Irritant contact dermatitis accounts for most cases of contact dermatitis and ACD is the second largest group [23]. Furthermore, in reality, often endogenous, irritant and allergic aetiologies coexist and give eczema. To diagnose irritant contact dermatitis, clinically relevant contact allergies have to be excluded. A diagnosis of contact dermatitis and ACD (Table 5.1.2) requires careful consideration of many variables and knowledge of the possible reactions of the skin to different substances.

The classical picture of ACD is that of erythematous papular, vesicular and/or scaly patches or plaques with margins corresponding to the area of contact, when active, the eczematous reaction may even develop outside the actual contact area. Eczema is the most common adverse reaction seen in an ACD patient, but other manifestations are possible, mainly depending on the allergen such as allergic contact granuloma, lichenoid eruptions, erythema multiforme, and lymphomatoid- and scleroderma-like eruptions [24–27]. It is most often found on the hands, arms and face, areas that are most often unprotected and in contact with many substances.

<table>
<thead>
<tr>
<th>Table 5.1.2 The diagnosis of ACD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Circumstances that enable the clinician to diagnose allergic contact dermatitis</strong></td>
</tr>
<tr>
<td>Establishing contact allergy</td>
</tr>
<tr>
<td>Exposure</td>
</tr>
<tr>
<td>Relevance</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

The exposure will define where the reaction is situated. Dermatitis in odd regions may thus occur (Table 5.1.3). Systemic contact dermatitis, i.e., when the allergen has on re-exposure reached the patient by the mucosae or has been injected, often gives a slightly different clinical picture. The clinical features of systemic contact dermatitis include flare-up of previous dermatitis or previously positive patch test sites, vesicular palmar and/or plantar dermatitis, flexural dermatitis, and the baboon syndrome [29].

Epicutaneous testing; i.e., establishing delayed hypersensitivity

Epicutaneous testing (Fig. 5.1.1), patch-testing, remains the gold standard for establishing the contact allergy. It has the advantage over in vitro techniques in that it is carried out on the skin, where possible metabolic reactions may occur and is also a sort of provocation test [28].

What should be tested?

The history (Table 5.1.4) and examination of a patient with suspected ACD will usually give clues to

<table>
<thead>
<tr>
<th>Table 5.1.3 Conditions when it is difficult to suspect the sensitizer from the history and clinical examination [28]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand eczema</td>
</tr>
<tr>
<td>Ectopic dermatitis</td>
</tr>
<tr>
<td>Airborne dermatitis</td>
</tr>
<tr>
<td>Connubial dermatitis</td>
</tr>
<tr>
<td>Multifactorial dermatitis</td>
</tr>
<tr>
<td>Systemic dermatitis</td>
</tr>
<tr>
<td>Noneczematous dermatitis</td>
</tr>
<tr>
<td>Atopy</td>
</tr>
</tbody>
</table>
possible sensitizers. Sometimes a totally unsuspected agent (Table 5.1.5) is found to be the sensitizer that causes the problems and a standard series has therefore been developed containing the most common allergens covering the most common exposures. In most countries commercially available standard series exist for this purpose, series that usually contain 20–25 test preparations, consisting of chemically defined compounds, mixes of allergens, and natural and synthetic compounds [30]. Epicutaneous testing should, if possible, be performed not only with the standard series that are commercially available and with special series according to the exposure of the patient but also when indicated, with the patient’s own material, and if the patient has a work-related eczema, with work-related material. To test with the patient’s own material demands chemical knowledge but increases the possibility of finding clinically relevant allergy substantially. If testing with own material, the physician needs knowledge of the chemical ingredients of the product, pH and whether the product contains agents that easily sensitize in order to decide on how the product should be tested. It is sometimes also necessary to acquire the constituents of a product to test these separately in order to get a diagnosis. Material Safety Data sheets are often helpful in this evaluation, but it may sometimes be necessary to get in contact with the company producing the product. Many substances have already been thoroughly investigated, and there also exist guidelines for how these should be tested [31].

The testing procedure

The patient should neither be sun burnt in the area of testing, nor should local corticosteroids be applied on the area [19] for 1 week prior to testing, and if possible, systemic steroids should not be used prior to testing. The chambers with the test materials are placed on the back with adhesives and removed after 48 h. If the patient is contact allergic to a tested substance an allergic contact eczema will develop. The tests can therefore be read after a certain period of time, based on the time interval between exposure and when the macroscopic eczematous reaction appears for the different allergens. For reasons of practicality, different standards for when readings should be performed have been developed [32]. In Sweden, readings are performed after 72/96 h and 1 week, the later reading being especially valuable.

---

**Table 5.1.4** When ACD is suspected the medical history of the patient is important to enable a correct epicutaneous testing and a correct diagnosis

<table>
<thead>
<tr>
<th>Important facts to ask for in the medical history of a patient with suspected ACD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hereditary factors</strong></td>
</tr>
<tr>
<td>Atopy own or relatives with atopic constitution</td>
</tr>
<tr>
<td>Other skin diseases</td>
</tr>
<tr>
<td><strong>Work</strong></td>
</tr>
<tr>
<td>What the patient does at work?</td>
</tr>
<tr>
<td>Exposure to possible allergens at work, not only work material but soaps, handcreams, etc.</td>
</tr>
<tr>
<td>Preventive measures tried at risk situations-protective equipment, gloves, etc.</td>
</tr>
<tr>
<td><strong>Home</strong></td>
</tr>
<tr>
<td>Wet work at home</td>
</tr>
<tr>
<td>Hobbies</td>
</tr>
<tr>
<td><strong>Time factor</strong></td>
</tr>
<tr>
<td>Aggravated when at work/at home/in special situations</td>
</tr>
<tr>
<td>Better/healed when on vacation or on sick-leave</td>
</tr>
<tr>
<td><strong>Medication and tried therapies</strong></td>
</tr>
<tr>
<td><strong>Known allergies</strong></td>
</tr>
</tbody>
</table>

---

**Table 5.1.5** Exposures that may cause difficulties in suspecting the sensitizer from history [28]

<table>
<thead>
<tr>
<th>Exposures that may cause difficulties in suspecting the sensitizer from history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concealed hazardous exposure; the patient does not know about the exposure</td>
</tr>
<tr>
<td>Infrequent hazardous exposure, may cause a transient intermittent dermatitis easily overlooked</td>
</tr>
<tr>
<td>No demonstrable hazardous factors, visits at work plants, if occupational dermatitis is suspected lessens this risk factor</td>
</tr>
</tbody>
</table>
for reactions that develop late such as those to gold and corticosteroids [19, 33]. Internationally, readings are usually performed on day 2 and 3/4. Today standardized criteria [34] for how the tests should be read have been developed (Table 5.1.6).

Once the patch testing has been performed, i.e., the contact allergy has been established, the relevance must be assessed before the diagnosis of ACD is established is a fact. Once epicutaneous testing has been performed the patient should be given oral and written information on all found contact allergens. The information should contain the chemical name, if cosmetics the INCI name (International nomenclature cosmetic ingredients), and possible synonyms. Usual ways of exposure for the chemical and if possible advice in avoiding it [35] should be given.

### 5.1.7 General Therapeutic Outline

If every allergen as well as substances that cross-react could be diagnosed, and if it was possible to avoid these substances, ACD would hardly be a problem, and therapy would seldom be necessary. Prevention is therefore very important!

### 5.1.7.1 Prevention

Primary prevention: This term includes the measures taken to avoid sensitization in the general society by controlling exposure. It is important that research (see experimental approaches) and legislation combine in this effort. A good example where this has worked is when iron sulfate was added to cement in order to reduce the amount of free chromate thus reducing the incidence of chromate-allergic individuals [36, 37]. If exposure cannot be limited, protective measures such as gloves and protective clothing are needed.

#### 5.1.7.1.1 Secondary Prevention and Tertiary Prevention

Secondary prevention includes the measures taken to prevent relapses of dermatitis in the hypersensitive individual. Sometimes, as in the case of primin hypersensitivity, the allergen in the flower Primula is easy to avoid and thereby the ACD heals.

#### 5.1.7.1.2 Why Secondary Prevention Often Does Not Work Sufficiently

The truth is that even if the allergen is diagnosed, it is often very difficult to avoid it completely. The reason for this is that some allergens are ubiquitous substances, used in different settings. Fragrances and formaldehyde are such examples. Fragrances are not only used in cosmetics but also in, for example, cleaning products. Even if the preservative formaldehyde is avoided there are other sources from which formaldehyde can be released, and complete avoidance is thus difficult. Avoiding an allergen also means avoiding possible cross-reacting substances; this may often be difficult since they may not be known. Compound sensitizers are the third problem; substances such as Myroxylon Pereirae where all possible allergens are not fully known, and also the fact that a substance might be chemically changed in the surroundings or in the skin to form allergens that cross react makes total avoidance difficult. The other most obvious reason for a person with an ACD that does not heal even if allergens are avoided is of course that the diagnosis wrong or that the patient, as is often the case particularly with hand dermatitis, is not only contact allergic but also suffers from irritant contact dermatitis and/ or atopic dermatitis. Other causes for sustained problems even if the allergen is topically excluded from the patient’s surroundings are ingestion of the allergen, as seen in

---

### Table 5.1.6 Grading of patch test reactions according to ICDRG (international contact dermatitis research group)

<table>
<thead>
<tr>
<th>Grading</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>?+</td>
<td>Doubtful reaction; faint erythema only</td>
</tr>
<tr>
<td>+</td>
<td>Weak positive reaction; erythema, infiltration, possible papules</td>
</tr>
<tr>
<td>++</td>
<td>Strong positive reaction; erythema, infiltration, papules, vesicles</td>
</tr>
<tr>
<td>+++</td>
<td>Extreme positive reaction; intense erythema and infiltration and coalescing vesicles</td>
</tr>
<tr>
<td>−</td>
<td>Negative reaction</td>
</tr>
<tr>
<td>IR</td>
<td>Irritant reaction</td>
</tr>
<tr>
<td>NT</td>
<td>Not tested</td>
</tr>
</tbody>
</table>
certain nickel-allergic patients. Occasionally the allergen has caused such profound damage and started a chronic eczematous reaction that does not heal even if the allergen is totally excluded, as may be seen in chromate-allergic patients [38, 39]. A correct diagnosis is however of utmost importance since many allergens can be avoided, or at least avoided to an extent that helps the patients clear their dermatitis, or that use of gloves or protective clothing may ensure healing.

5.1.8 Current Established Therapies

The actual medical treatment for ACD does not differ from that of eczema of other etiologies. Hyposensitization has proven difficult in ACD. Oral hyposensitization has appeared efficacious in experimental trials for a few allergens such as nickel and urushiol [40]. This hyposensitization is antigen-specific and short-lasting. Both clinical and experimental findings indicate that full and persistent tolerance can only be induced prior to any sensitizing contact [41–43].

Topical corticosteroids are frequently the first line of pharmacologic therapy for those with ACD where the allergen cannot be avoided or where the etiology is mixed.

5.1.9 Experimental Approaches

Much research in the field of ACD is done to find potential allergens, to explore the sensitizing potential, and to find whether a contact allergen is relevant to the dermatitis of the patient. If an allergen is found, ubiquitous research can be performed to find a less sensitizing equivalent chemical, or if possible, to eliminate the exposure where sensitizing is possible as was done with chromate [37], where the addition of iron sulfate to cement reduces most of the hexavalent chromium to an insoluble trivalent salt.

As in other fields of medicine there is a need for models to enable testing of substances and prediction of how the substances will act in humans. It goes beyond the chapter of this book to focus on the different test techniques and therefore the emphasis is put on the human in vivo testing techniques, especially since the epicutaneous testing as such can be seen as a provocation model performed in the actual patient.

5.1.9.1 Identifying a Substance

There are several techniques to identify substances in a sample such as high-performance liquid chromatography (HPLC), atomic absorption spectrophotometry, and mass spectrometry. These techniques require a chemical laboratory and are primarily used in experimental settings. Since the aim of this chapter is to give further knowledge of ACD the identification of substances as such will not be discussed. The techniques can be studied in greater detail as to how they are used and for what in the field of ACD, in the literature on the subject of contact dermatitis [44].

5.1.9.2 In Vivo Testing in Humans

5.1.9.2.1 Serial Dilution Test

To quantify the elicitation response in humans the most commonly used test is the serial dilution test where epicutaneous testing is performed with the substance to be tested in several dilutions, usually with a concentration span covering a factor of at least 100 [45]. Thresholds are determined as the minimal elicitation concentration (MEC) or as the maximum no effect level (NOEL). A problem is that besides interindividual variation there is also an intraindividual variation in reactivity over time.

The test is useful for determining the optimal test concentration of a substance [46, 47] and to help assess the clinical relevance [48].

5.1.9.2.2 Repeated Open Application Test (ROAT) [47]

Repeated open application of a potential allergen to the same area of skin (usually to the upper or lower medial aspect of the arm); the skin on the neck and face can also be used for ROAT. Usually. The allergen is applied twice daily for 14 days. ROAT can be used on groups of patients to investigate whether repeated
application of a weak allergen or an allergen in low concentration still evokes ACD and thus find a tentative concentration limit for elicitation. It is also a model to imitate the common use of a product/allergen and can thus be used to find the potential clinical relevance of an allergen. It is also a useful method to take into the evaluation where the product is used, i.e., the test can be modified for use in the axillae (Fig. 5.1.2) or on fingers [47–52].

Many sensitizers may contain several allergens, such as the perfume substance oakmoss [53]; an allergen may contain impurities and sometimes the substance we test with is not what is labeled [54]. A method to investigate the purity of a substance is by thin layer chromatography [44, 55, 56].

5.1.10 Complications to Avoid

ACD is a disease that may mimic many other eczematous diseases and it is therefore important to keep the diagnosis in mind and to be liberal in referring or performing epicutaneous testing. Many patients have both ACD, endogenous and irritant contact dermatitis. The patient’s history is important since this may give clues to what allergens should be tested; if this is not diligently performed contact allergies may very well be missed. A good knowledge of chemistry is desirable in order to perform good epicutaneous testing. Present exposure and assessment of relevance are of the utmost importance; a contact allergy as such does not mean that a patient has ACD.

5.1.11 Global Variations

Publications on contact allergies that generate incidence-type data in the general population are scarce; an exception is the Copenhagen Allergy study [57]. These data are though important since data generated from patients with dermatitis risk being too high, as patients risk sensitization through their dermatitis [58]. Also here it is important to differentiate between contact allergy and ACD since a known frequency of contact allergy to a substance does not indicate that a dermatitis in the same population is caused by this allergen. From this point of view, instead of discussing global variations in ACD which implies a difference through ethnicity, which has so far not been shown, other variations in ACD should be given more importance. ACD will differ according to exposure which also inflicts the frequency of contact-allergic individuals in various countries. Because of differences in use of, for instance, preservatives, the frequency of contact allergy will differ in various countries; one such example being methyl dibromoglu taronitrile, where the use for a period was high in Europe but low in the United States. Contact allergy to Ambrosia artemisifolia, ragweed, is a common cause of contact dermatitis in North America and India and much less
common in Sweden [59]. Various employments have different risk factors for contact allergic dermatitis. Legislation aiming for decreased levels of possible allergens or a higher degree of protection at work or well implemented skin care programs, which may reduce the contact allergy frequency or irritant contact dermatitis, is thus of utmost interest. A decrease of contact allergy to nickel has been shown after the legislation regarding the allowed amount of nickel in alloys was restricted [60], and similarly the frequency of contact allergy to chromate has decreased after the protective measure of adding iron sulfate to concrete was performed in the Nordic countries [37]. Occupational dermatitis will be discussed elsewhere but there are different high risk occupations for contact allergic dermatitis, for example, hairdressers, bakers, and florists [61–63].

References


44. Orbanjea JG, Dicz L, Lonzano J et al (1976) Lymphomatoid contact dermatitis: a syndrome produced by epicutaneous hypersensitivity with clinical features and a histopathologic picture similar to that of mycosis fungoides. Contact Derm 2:139–143


5.2 Principles of Photosensitivity Diseases

Photosensitivity diseases include a variety of disorders with diverse pathomechanisms, etiologies, action spectra of light, and clinical manifestations. Any photobiological reaction can occur only when a certain photochemical reaction takes place. According to the primary law of photochemistry, (Grotthus-Draper’s law), photons must be absorbed by molecules to initiate photochemical reactions. The light-absorbing molecules are called chromophores. Then, a chromophore that absorbs light energy of action spectrum must exist in the skin to start a response of the skin to light. There is no generally accepted classification of photosensitivity diseases. Based on the origin of responsible chromophores or photosensitizers, photosensitive disorders can be classified broadly into endogenous and exogenous photosensitivity diseases (Table 5.2.1). Among them, solar urticaria, polymorphous light eruption (PLE), chronic actinic dermatitis (CAD), and drug-induced photosensitivity are described in this section. Representative endogenous photosensitivity dermatoses including xeroderma pigmentosum, Cockayne’s syndrome, and porphyria will be described in other chapters.

5.2.2 Evaluation of Photosensitive Patients

Before the identification of the type of photodermatosis, it should be examined if the presenting clinical conditions are actually related to sun exposure. A careful history-taking is most important for the evaluation. Most of photosensitive patients recognize a climatic or seasonal variation in the severity and extent of their conditions. The age at onset of the eruption may be suggestive of some photosensitivity diseases which appear congenitally, in childhood, in adulthood, or in the aged. A medication history should be carefully obtained. The physical examination of the distribution pattern of lesions is useful to take photosensitivity into consideration. Exposed skin areas including the face, ears, nape of the neck, “V” area of the chest, dorsal hands, and extensor aspects of the forearms are commonly involved. In contrast, although uncovered, web spaces of the fingers, submental area, and posterior auricular area are usually uninvolved. Areas protected

---

T. Horio
Department of Dermatology, Kansai Medical University, Fumizono 10-15, Moriguchi, Osaka 570-8507, Japan
e-mail: horio@takii.kmu.ac.jp
by a watch, ring or hat may be also spared. These characteristic patterns of distribution are useful for the differential diagnosis of airborne contact dermatitis.

### 5.2.3 Phototesting

Phototesting can induce a miniature of skin lesions in patients with suspected photosensitivity disease by means of irradiation with artificial light sources. The existence of photosensitivity, precise diagnosis, action spectrum, or etiologic factors can be confirmed when the characteristic skin changes are reproduced in phototesting. The testing is useful for several photosensitivity diseases, listed in Table 5.2.2.

#### 5.2.3.1 Light Source

The light source for phototesting should have adequate irradiance in the action spectrum of the disease being examined. Otherwise, phototesting may yield a false negative result. The emission spectrum should be in the long-wave ultraviolet light (320 < UVA < 400 nm), mid-wave ultraviolet light (290 < UVB < 320 nm), or visible light (400–500 nm) range. The light source for in vivo testing should not emit short-wave ultraviolet light (UVC < 290 nm), which is not included in the natural sunlight and may induce a false positive reaction. Furthermore, it is desirable that the light source be easily and economically available for practice use.

Fluorescent tubes are useful and convenient light sources for UVA and UVB irradiation. The so-called black light and sunlamp produce irradiation primarily in the UVA and UVB ranges, respectively. However, it should be remembered that small amounts of UVB and UVA are also emitted from the black light and sunlamp, respectively. These fluorescent tubes have a field size large enough to test a number of materials at once in photopatch testing. A slide projector can be used as a visible light source to specially examine solar urticaria.

#### 5.2.3.2 UVA Irradiation

The UVA-sensitive photodermatoses include drug-induced photosensitivity, photocontact dermatitis, CAD, certain cases of PLE, hydroa vacciniforme, and some cases of solar urticaria (Table 5.2.2). The irradiation dose to reproduce the clinical lesion depends on the severity of photosensitivity in the patients, and therefore varies not only among diseases, but also among patients of an identical disease.

For example, UVA at doses of 1.5, 3.0, 6.0, and 9.0 J/cm² is exposed to four areas (2 × 2 cm each) on normal-appearing skin using fluorescent black light tubes. Exposed areas are read 24 and 48 h after irradiation. Only the patients with possible solar urticaria are evaluated until 30 min after exposure. In normal subjects, the UVA exposure under this condition does not produce any reaction, except immediate pigment darkening, which disappears within a few hours of irradiation. Therefore, an erythematous reaction can be estimated as an abnormal photosensitive state.
5.2.3.3 UVB Irradiation

The UVB-sensitive photodermatoses are less common than the UVA-reactive diseases. The UVB radiation easily produces sunburn reaction even in normal persons. Therefore, it is not always easy to interpret the reaction induced by UVB irradiation because the photosensitive patients can develop pathological changes mixed with a physiological reaction. The reactions should be evaluated quantitatively and qualitatively.

5.2.3.4 Visible Light Irradiation

Phototesting with visible light source is of diagnostic value, especially in solar urticaria, whose action spectrum lies in this range. A slide projector is an easily available and valuable light source for provocative phototesting.

5.2.4 Photopatch Testing

5.2.4.1 Indication

Photopatch testing is performed in order to reproduce the photoallergic contact dermatitis in miniature by topical application of the suspected photosensitizer and subsequent exposure by activating ultraviolet light. Photopatch testing may be valuable in some patients who are photoallergically sensitized by systematically administered drugs.

5.2.4.2 Procedure

Photopatch testing is performed with the following procedure, although certain modifications may be made:

1. Application of chemical substances in duplicate patches
2. Covering of patches with light opaque material
3. Evaluation of uncovered patches 48 h later
4. Irradiation of one set of patches with UVA
5. Covering of both sets
6. Evaluation after an additional 24, 48, and 72 h

Test materials must be selected to be examined based on the information from the patient’s history. The chemical substances listed in Table 5.2.3 are often used as the photopatch test series. Test materials must be used in nonirritating and nonphototoxic concentrations. The action spectrum of photoallergic contact dermatitis is primarily in the UVA range. A bank of multiple black light lamps is convenient equipment for this purpose. Test sites are irradiated with 1–5 J/cm² or with 50% of the threshold dose of UVA.

5.2.4.3 Evaluation

Results of photopatch testing are evaluated together with another set of patch testing. When a positive reaction was induced at the irradiated patch and a negative one at the nonirradiated patch of the identical material, the result is interpreted as the presence of photoallergic contact dermatitis. If both sites show equally positive reactions, plain contact dermatitis is present because the light exposure does not play any role in the reaction. In a few cases, both irradiated and nonirradiated sites show positive results, but the former reaction is more pronounced than the latter, indicating a coexistence of allergic and photoallergic contact dermatitis to the same chemical.

5.2.5 Drug Phototesting

Photopatch testing may be of no value in the diagnosis of photosensitivity reaction induced by systematically administered drugs. In principle, the causative agent should be administered through the same route as in the clinical use to reproduce the reaction. Drug phototesting is performed according to the following steps in our photodermatology clinic:

1. Determination of photoreactivity especially to UVA during drug intake
2. Discontinuation of drug intake for 1 week
3. Determination of photoreactivity
4. Readministration of drug for 1 day
5. Reexamination of photoreactivity
6. Comparison of photoreactivity at each step
When the photoreactivity during drug intake is significantly reduced after drug discontinuation and is enhanced again after readministration, the drug can be estimated as the responsible photosensitizer. The above-mentioned procedure must be modified depending on the sensitizing drugs, degree of patient’s photosensitivity, and type of eruption.

5.2.6 Solar Urticaria

5.2.6.1 Etiology and Pathophysiology

Solar urticaria can be passively transferred to normal subjects by means of an intradermal injection of patient’s serum and subsequent light exposure of injected skin [1]. The passive transfer test in solar urticaria is a modification of the Prausnitz-Kustner technique classically used in immediate hyper-sensitivity reactions. A positive result suggests that a specific IgE antibody to the urticaria development may exist in the patient’s serum. Most patients with solar urticaria develop an urticaria reaction at the site of injection of their own sera, which have been previously irradiated at the action spectrum in vitro (Fig. 5.2.1) [2, 3].

The irradiated patient’s serum does not produce the urticaria reaction in normal subjects. Therefore, the photoresponse is specific to the patients with solar urticaria, in other words, it may not be a phototoxic reaction. This is supported by the positive passive transfer test, as described above. Based on these findings, solar urticaria seems to be an autoimmune disease due to an immediate type of photoallergic reaction [4]. The responsible photosensitizer has not been clearly identified. Using the ultrafiltration technique, we indicated that a serum factor with molecular weight more than 100 KDa in one patient [3] and more than 300 KDa in another [5] might be transformed to the photoallergen after irradiation. Although the wheal-forming factor may be produced from an endogenous serum factor in most patients, solar urticaria can be induced very rarely by exogenous factors such as chemical substances. One of our patients with solar urticaria showed an immediate type of photoallergy to chlorpromazine [6].

### Table 5.2.3 Causative drugs for photosensitivity

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antimicrobials</strong></td>
<td></td>
</tr>
<tr>
<td>New quinolones</td>
<td>Fleroxacin, lomefloxacin, sparfl oxacin, enoxacin, ofloxacin</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Demethylchlortetracycline, doxycycline</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Sulfanilamide</td>
</tr>
<tr>
<td><strong>Antibacterials</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tribromosalicylanilide, bithionol, hexachlorophene</td>
</tr>
<tr>
<td><strong>Antifungals</strong></td>
<td>griseofulvin</td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
<td>Chlorothiazide, hydrochlorthiazide, furosemide</td>
</tr>
<tr>
<td><strong>Antipsychotics</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chlorpromazine, perphenazine, levomepromazine, prochlorperazine, thioridazine</td>
</tr>
<tr>
<td><strong>Hypoglycemics</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tolbutamide, chlorpropamide</td>
</tr>
<tr>
<td><strong>Antihistamics</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Promethazine, diphenhydramine, mequitazine</td>
</tr>
<tr>
<td><strong>NSAIDs</strong></td>
<td>Piroxicam, naproxen, benoxaprofen, ketoprofen, suprofen, tiaprofen</td>
</tr>
<tr>
<td><strong>Anticancers</strong></td>
<td>5-fluorouracil, tegafur, dacarbazine</td>
</tr>
<tr>
<td><strong>Cardiacs</strong></td>
<td>Quinidine diltiazemhydrochloride</td>
</tr>
<tr>
<td><strong>Fragrances</strong></td>
<td>musk ambrette, methylcoumarin, 8-methoxypsoralen, trimethylpsoralen</td>
</tr>
<tr>
<td><strong>Psoralens</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Muscle relaxant</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Anesthetics</strong></td>
<td>afoqualone, dibucaine</td>
</tr>
<tr>
<td><strong>Sunscreens</strong></td>
<td>Para-aminobenzoic acid (PABA) octyl dimethyl PABA, amyl dimethyl PABA, oxybenzone, sulisobenzene, octyl methoxyccinnamate, butyl methoxydibenzyol-methane</td>
</tr>
</tbody>
</table>
5.2 Photosensitivity Diseases

5.2.6.2 Clinical Characteristics and Diagnosis

Solar urticaria develops localizing wheals at the site of exposure to sunlight usually within a few minutes. When the exposure time is short, the wheal may be minimal or absent and only erythema develops. Within a few hours, the urticaria disappears completely without any residual skin changes similar to other types of urticaria. When large areas of the body are exposed to sunlight for a long period of time, systemic signs such as dizziness, sleepiness, wheezing, dyspnea, and systemic collapse can occur. Regularly sun-exposed skin, such as the face, the dorsal hands, and the extensor aspects of the forearms, are often less sensitive than covered body areas. In summer months, solar urticaria may develop on covered parts of the body as a result of small amounts of light penetrating thin clothing. In visible light-sensitive patients, artificial room light can produce urticaria.

Fig. 5.2.1 The patients with solar urticaria develop a wheal reaction at the site of injection of their own sera which have been previously irradiated in vitro

Clinical features of solar urticaria are so characteristic that it is not difficult to make a possible diagnosis from the patient’s history. However, skin changes of solar urticaria are not always observed when the patients visit dermatologists, since sunlight-induced wheal lasts only for a short time. Therefore, to make an accurate diagnosis urticaria reaction should be provoked by light exposure using the sunlamp, black light, and slide projector lamp.

Usually an erythema or wheal reaction appears within 5–15 min after termination of the irradiation (Fig. 5.2.2).

5.2.6.3 General Therapeutic Outline

Elimination of causative agent is very difficult in solar urticaria, because the photosensitizer is of endogenous origin in the majority of patients. For the treatment of
urticaria, the prevention of its development is required, since the wheal, once appearing, spontaneously subsides in a short time.

Solar urticaria might be induced by an immediate type of hypersensitivity mediated by IgE antibody. Therefore, the main chemical mediator for skin changes must be histamine released from mast cells in the skin. Increased histamine levels have been reported in venous blood draining the skin where urticaria had been induced [5, 7, 8]. Systemic use of antihistamines, H1 receptor antagonists, has a beneficial effect to some degree, reducing the wheal and itching. Other medications, phototherapy and light-shielding may be useful in some patients. For the treatment of solar urticaria, a single use of any modality is not satisfactory to obtain complete prevention. Combination therapy should be performed depending upon photobiological characteristics of the patients.

5.2.6.4 Current Established Therapies

Antihistamines: Chlorpheniramine [9] and homochlorcyclizine hydrochloride [10] have been systemically used for the treatment of solar urticaria. Newer H1 receptor antagonists such as terfenadine [11] and astemizole [12] seem to be more effective. Holzle described that all antihistamines failed in highly photosensitive patients, although they were helpful in combination with other therapies or for patients with low or moderate photosensitivity [13].

Desensitization by repeated irradiations: Skin constantly exposed to natural sunlight and also an area where urticaria has recently been produced is tolerant to subsequent irradiation. Repeated exposures to natural sunlight or to the action spectrum from artificial light sources often show beneficial effects [14]. The treatment must be performed at an interval of a few days increasing the exposure dose. To avoid systemic and severe local side effects, caution must be taken not to expose too large an area, and not increase the dose too rapidly.

PUVA: Photochemotherapy with psoralen and UVA (PUVA) has also been used with beneficial effect [15, 16]. The tolerance induced by PUVA therapy lasts longer than that obtained by desensitizing phototherapy. PUVA therapy is effective not only in UVA-sensitive patients, but also in those where the action spectrum does not include the UVA range. Sunscreen: Broadband suncreening agents that contain not only UV absorbing chemicals but also physical blockers such as titanium dioxide and zinc oxide are somewhat helpful for UV-sensitive patients, but unsatisfactory for visible light-sensitive patients. Sunshading by the use of clothing, hat and gloves is more useful in preventing wheal development.

5.2.6.5 Experimental Approaches

Action spectrum: The eliciting wavelengths (action spectrum) of solar urticaria are different among cases from UVB to visible light. This suggests that chromophores or photosensitizers responsible for solar urticaria are not uniform in all patients. In our series of 42 cases, 24 patients (57%) were sensitive only to visible light, which was the most common action spectrum. Other patients reacted to UVA and/ or UVB. Four patients were sensitive to a wide spectrum from UVB to visible light.

Inhibition spectrum: The wheal formation induced by exposure to action spectrum light can be inhibited by additional irradiation with other spectrum [17]. Wavelengths of inhibition spectrum are usually longer but rarely shorter than those of action spectrum [4]. In some patients, wheal formation is inhibited only when the skin is exposed to action spectrum and then to inhibition spectrum, while in other patients, exposures before as well as after exposure to the action spectrum showed inhibitory effect. Furthermore, only pre-exposure may be effective in rare cases.

Augmentation spectrum: We found that wavelengths outside the action spectrum could enhance wheal development [4, 5]. The action spectrum was defined in the 320–420 nm in this patient. An exposure to longer wavelengths at 450–500 nm increased the reaction to 320–420 nm before but not after irradiation at the action spectrum. Therefore, irradiation at 450–500 nm showed an augmentative rather than an additive effect with 320–420 nm light. If additive, the postirradiation exposure should have the same effect as the pre-irradiation exposure. An augmentation spectrum has been recognized only in 4 of 14 cases examined in our series.

The action modes and clinical relevances of inhibition and augmentation spectra have not been clarified.
Various wavelengths, including action, inhibition and augmentation spectra, may exert complicated effects each on wheal formation in solar urticaria.

### 5.2.6.6 Complications to Avoid

Anaphylaxis can occur in extremely photosensitive patients. Sunlight exposure for a long time period or to large area of the skin should be avoided in such patients.

### Take Home Messages

- The characteristic feature of solar urticaria is an immediate wheal reaction to sunlight.
- Action spectrum varies among patients.
- Repeated exposures to light can induce desensitization.

### 5.2.6.7 Global Variations

Solar urticaria appears throughout the world in any race and in any geographic region. Patients in European countries have been reported to be activated most frequently by UV radiation. In contrast, Japanese patients are commonly sensitive to visible light.

### 5.2.7 Polymorphous Light Eruption

#### 5.2.7.1 Etiology and Pathophysiology

The pathomechanism of PLE is still unknown. There may be a variety of mechanisms or etiologies involved that may account for the polymorphous clinical appearances. PLE is defined as recurring, pruritic eruptions, precipitated by sunlight, but unrelated to exogenous photosensitizing drugs [18]. The photosensitivity in this disease is a clinically delayed response to sunlight, which appears after a latent period of hours to days. The consistent histological finding in PLE is a perivascular infiltrate composed mainly of T lymphocytes. These features suggest that PLE might involve cell-mediated immune mechanisms in which sunlight-induced self-antigens might trigger a delayed-type hypersensitivity reaction, as Epstein first postulated [19]. The action spectrum of PLE varies among patients. Some studies have shown that UVB radiation was most effective in reproducing skin changes [20, 21], while other investigators claimed that UVA [22] or UVA plus UVB [23] provoked typical reactions.

#### 5.2.7.2 Clinical Characteristics and Diagnosis

Clinical features of PLE vary from eczema to papules, vesicles, plaques, insect bite-like and erythema multiforme-like lesions. However, they are usually monomorphous in the individual patient. Eczematous and papular forms are the commonest (Fig. 5.2.3). PLE commonly appears in spring or early summer following the first exposure to strong sunlight after the cold season. During summer the eruptions may become less
severe and tolerant to sunlight. This phenomenon is known as “desensitization” or “hardening.” Reproduction of the lesion by phototesting is of diagnostic value.

5.2.7.3 General Therapeutic Outline

The therapeutic outline for PLE includes the symptomatic therapy of existing lesions, the prophylactic treatment, and the protective light shielding. Usually topical treatment is satisfactory for the acute exacerbation of eruptions, since general conditions are not affected in this disease.

5.2.7.4 Current Established Therapies

The topical application of corticosteroids is useful for the treatment of PLE. Milder lesions respond well to topical tacrolimus. Severe cases may be satisfactorily treated with a brief course of oral corticosteroids. The prophylactic effects of photo (chemo) therapies have been reported in severe conditions of PLE. Especially the efficacy of PUVA treatment has been well established by several studies [24, 25, 26]. The schedule of PUVA treatment consists of three treatments per week for 3–4 weeks, starting 1 month prior to the expected sun exposure [23]. Thereafter, patients are advised to have regular repeated sun exposure to maintain protection. Total protection can be obtained during outdoor activities in the summer. Broad-band [27], narrow-band UVB [28] or UVA phototherapy [29] has been reported as also being effective in the prophylaxis. Topical application of sun-screening agents which absorb in UVA and UVB range is helpful to protect the development of PLE. Patients who do not have complete prophylaxis need to cover the skin by clothes.

5.2.7.5 Experimental Approaches

Skin change similar to PLE has been produced in experimental animals [30, 31]. Guinea pigs, which had been repeatedly irradiated with UVA following injections of Freund’s complete adjuvant but without application of chemical photosensitizers, showed eczematous reaction after exposure to a smaller amount of UV radiation.

5.2.7.6 Global Variations

Small papules may develop as one of the commonest forms of PLE. Elpern reported a distinctive type of PLE designated as papulovesicular light eruption which was seen commonly in tourists visiting Hawaii from the mainland United States or Canada [32]. The eruption consisting of monomorphous papules, papulovesicles, or vesicles, mainly affected young to middle-aged white women. Subsequently we described a similar form, which consists of monomorphous small papules in Japanese children or women, under the name of micropapular light eruption. Later Kontos et al reported that the similar type of PLE may manifest as a pinpoint popular variant in individuals with highly pigmented skin [33].

5.2.8 Chronic Actinic Dermatitis

5.2.8.1 Etiology and Pathophysiology

CAD is commonly included in the idiopathic photodermatoses because the underlying mechanism remains unknown. Allergic or photoallergic contact dermatitis to multiple allergens frequently co-exists with CAD. A transition can occur from photoallergic contact dermatitis to CAD [34]. The histologic features of CAD are primarily eczematous changes showing epidermal spongiosis and dense perivascular lymphocytic infiltration, sometimes associated with atypical lymphocytes with large, convoluted nuclei or mitotic figures. CAD is clinically and histologically compatible with the process of delayed type of hypersensitivity. A number of
possible triggering factors of CAD development have been proposed, including the persistence of photocontact-sensitizers in the skin, an autosensitization to autologous proteins following photoallergic dermatitis, a reaction to kynurenic acid acting as an endogenous photosensitizer, or an alteration in immune regulation [35]. Patients react abnormally to UVB, often also to UVA, and occasionally to visible light range.

5.2.8.2 Clinical Characteristics and Diagnosis

CAD is a disabling eczematous eruption with extreme photosensitivity affecting predominantly elderly men [36] (Fig. 5.2.4).

The eruption frequently spreads to affect the covered areas, and erythrodermatous condition may sometimes occur in patients with severe disease. The infiltrated plaques may resemble cutaneous T-cell lymphoma. In contrast to other photosensitivity diseases, palms and soles are also affected in some cases. Approximately 90% of patients are men with an average age of 65 years. In addition to clinical and histological features, an extreme photosensitivity to broad range of light is diagnostic of CAD.

5.2.8.3 General Therapeutic Outline

Therapeutic outline of CAD includes suppression of highly enhanced immunologic reaction and protection of sunlight exposure. To avoid adverse effects, immunosuppressive therapies should be carefully used for chronic diseases in elderly patients.

5.2.8.4 Current Established Therapies

Topical medication: Topical application of steroids is a generally helpful therapy. Steroid preparations should be selected depending upon the severity of eruptions and on the site of application. Strong steroids are used to heavily lichenified lesions on the dorsal hands and the nape of the neck, and less potent agents to other parts of the body. A prolonged use of strong steroids, especially to the face, can induce skin atrophy and telangiectasia. In such cases, topical tacrolimus is useful [37].

Systemic medications: Short-term oral steroid therapy is helpful to suppress acute flares. Oral immunosuppressants such as azathioprine (1.0–2.5 g/kg) [38, 39] or cyclosporine (3.5–5.0 mg/kg) [40] may be administered in selected patients. Two thirds of patients who tolerated the azathioprine intake obtained complete remission or marked improvement.

PUVA therapy: Patients with severe CAD may improve with psoralen plus UVA (PUVA) therapy [41, 42]. Oral PUVA treatment twice weekly starting with a UVA dosage of 0.25 J/cm and increasing gradually to a maximum of 10 J/cm was successfully used for CAD patients by Hindson et al [41].

Sun protection: Sufficient clothing cover and high-protection sunscreens containing chemical absorbers and physical blockers are generally necessary.

5.2.8.5 Experimental Approaches

Severe cases of CAD may be clinically and histologically indistinguishable from cutaneous T cell lymphoma (CTCL). CD4+: CD8+ ratio in circulating
lymphocytes may be helpful indistinguishing these two conditions. CD8+ lymphocytes are predominant in CAD, while CD4+ cells in CTCL. Although there have been isolated reports of coexistence of CAD and CTCL, it is unclear whether these rarities are incidental occurrences, confusions in diagnosis or casual associations, as Menage and Hawk described [35].

5.2.8.6 Global Variations

Although there is a geographical variation in the incidence, CAD can affect all races. CAD has been reported in patients with human immunodeficiency virus infection [43].

5.2.9 Drug-Induced Photosensitivity

5.2.9.1 Etiology and Pathophysiology

Drug photosensitivity reactions can be divided into phototoxic and photoallergic reactions based on the mechanisms involved, whether nonimmunological or immunological. The mechanisms of action of phototoxic reaction is not uniform, depending on the responsible chemicals. Phototoxic substances can lead to destruction of cell membranes, lysosomes, mitochondria, and/or nucleus. Drug-induced photoallergy usually involves a delayed type of hypersensitivity. It is especially well established that photoallergic contact dermatitis develops just like allergic contact dermatitis through a T cell-mediated immunologic reaction. A single drug may cause phototoxic as well as photoallergic reactions. The action spectrum of drug-induced photosensitivity lies within UVA range in most instances. Representative drugs which cause photosensitivity are listed in Table 5.2.3.

5.2.9.2 Clinical Characteristics and Diagnosis

Phototoxic reaction: Phototoxic reactions can occur theoretically in any subject if sufficient doses of the drug are administered and appropriate wavelengths (action spectrum) of light are irradiated. The clinical features of drug-induced phototoxicity are varied. Most commonly, patients develop a tender erythema, edema, and sometimes blisters associated with burning sensation (Fig. 5.2.5). These changes resolve within a few days accompanied by desquamation and hyperpigmentation. Less common manifestations include lichen planus-like photosensitivity, 44–46] and
5.2 Photosensitivity Diseases

pseudoporphyria [47–49]. However, a photoallergic process was suggested in some cases of lichen planus-like photosensitivity [50].

The diagnosis of phototoxic reaction is more difficult than that of photoallergic reaction. History of exposures to phototoxic drugs and photodistribution of eruptions are of benefit in establishing the diagnosis. Photopatch testing and drug phototesting cannot be applied for diagnosis or to prove the cause of phototoxic dermatitis, because phototoxic reaction is not specific to photosensitive patients, but can occur in all normal persons.

Photoallergic reaction: Either systemically or topically administered agents can induce photoallergic reaction. A photoallergic reaction is induced with fewer doses of the drug and light than a phototoxic reaction. Drug-induced photoallergic responses are usually eczematous (Fig. 5.2.6), but rarely lichen planus-like eruptions may occur. Some patients may retain a persistent reactivity to sunlight that continues long after the exposure to the causative photosensitizing drug has ceased. These patients are called persistent light reactors. Diagnosis and causative drugs can be defined by drug phototesting or photopatch testing. Test materials are selected based on history of drug intake.

5.2.9.3 General Therapeutic Outline

Avoidance of offending sensitizers is essential for the treatment of drug-induced photosensitivity. Photoallergic reactions last longer than phototoxic reactions. Until the photosensitivity subsides, especially in persistent light reactors, symptomatic therapy and sun-protection are necessary.

5.2.9.4 Current Established Therapies

Cool compresses and topical emollients are usually helpful for the treatment of phototoxic dermatitis. Topical steroids with appropriate potency are used depending upon the severity of eruptions and sites of application for the symptomatic therapy of photoallergic dermatitis. Persistent light reactors additionally need sun-protection with clothing cover, and sunscreens.

Take Home Messages

- Drug-induced photosensitivity can be classified into phototoxic and photoallergic reactions.
- The action spectrum lies primarily in UVA range.
- A photoallergic reaction is induced with fewer doses of the drug and light than a phototoxic reaction. Persistent light reaction may develop from photoallergic dermatitis.

References

44. Harber LC, Lashinsky AM, Baer RL (1959) Skin manifestations of photosensitivity due to chlorothiazide and hydrochlorothiazide. J Invest Dermatol 33:83−84
5.3 Drug Reactions

Hans F. Merk and Daniela Höller Obrigkeit

Key Features

- A large number of adult population suffer from undesired side effects to pharmaceutical products during the course of their lives. These reactions can be classified as expected or A-type reactions and unexpected or B-type reactions. The skin is a preferred target organ for B-type reactions. This type of skin reactions occur in 2–3% of hospitalized patients. Morbilliform drug rashes are the most often occurring skin reactions to drugs, constituting up to 90% of all reactions, followed by drug-induced urticaria, which constitutes about 6%. Severe cutaneous adverse reactions (SCAR) to drugs include:
  - Anaphylaxis and angioedema
  - Photosensitivity
  - Drug-induced hypersensitivity syndrome (DIHS)/drug reaction with eosinophilia and systemic symptoms (DRESS)
  - Bullous drug reactions, including toxic epidermal necrolysis (TEN)
  - Most often involved drugs are
  - Antibiotics – in particular β-lactam antibiotics, sulphonamids and fluoroquinolones
  - Antiretroviral drugs, such as abacavir and nevirapin
  - Allopurinol
  - Anticonvulsants
  - Contrast media
  - NSAIDs
  - Cytotoxic drugs such as platinum salt hypersensitivity
  - Investigations about the functions of mediators and their effects in immediate type reactions such as anaphylaxis as well as signs and symptoms e.g., of angioedema improved our understanding of these reactions and revealed three main mediator systems:
    - Histamine release
    - Derivatives of arachidonic acid
    - Bradykinin (angioedema)
  - T-cells in delayed-type reactions and differently expressed cytokines improved our understanding of the pathophysiology of allergic reactions, and led to new diagnostic options and therapeutic concepts. Recently established animal models as well as investigations on the level of antigen-presenting cells may improve the ability to predict the immunogenicity of small molecular weight compounds.

5.3.1 Introduction

About 26% of the adult population suffers from undesired side effects of pharmaceutical products during the course of their lives [1]. Depending on the pharmacological properties of a drug, reactions can be rated as A-type reactions (expected reactions) or...
B-type reactions (unexpected reactions). A-type reactions comprise drug toxicity, for example, overdosage or inevitable side effects at a dosage necessary to achieve the desired effect as in the case of chemotherapeutic agents and drug interactions. Examples of A-type reactions appearing as skin diseases include alopecia induced by chemotherapy, folliculitis induced by anti-EGF treatment, or severe dryness of the skin induced by retinoid treatment.

B-type reactions result from the specific properties of each active pharmaceutical ingredient (API) and individual risk factors of the patient. These reactions include: (1) intolerance reactions – side effects that occur at low concentrations of a drug, (2) idiosyncracy reactions – reactions depending upon patient-specific genetic or pharmacokinetic characteristics as well as (3) allergic or (4) pseudoallergic reactions.

An allergic reaction requires a specific T-cell-dependent allergization of the patient leading to a T-cell- or antibody-dependent allergic reaction. Pseudoallergic reactions mimic clinical patterns of allergic reactions; however, a specific allergization to a drug is not necessary. The term pseudoallergic reaction is controversially discussed, since overlaps with other reaction types occur. For example, a pseudoallergic reaction to non-steroidal anti-inflammatory drugs is understood as an intolerance reaction, since the pathophysiological basis of this reaction is based upon the expected pharmacological effect of COX-inhibition.

The focus of this overview is on skin, where allergic and pseudoallergic reactions frequently occur.

5.3.2 Epidemiology

In 3–9% of all hospitalized patients, side effects are a reason for inpatient treatment. Up to 81% of all hospitalized patients suffer from pharmaceutical side effects, and 26% of all adults suffer from an allergic or pseudoallergic drug eruption during the course of their lives [1, 2]. In a prospective study over a time period of 6 months, undesirable skin reactions to drugs were seen in 3.6:1,000 hospitalized patients [3].

At an assumed side effect incidence rate of 1 in 10,000, at least 30,000 patients needed to be treated with a medication to detect an assurance level of 0.95 for a particular side effect. In contrast, only 5,000 patients are typically exposed to an API during clinical trials leading up to approval [4]. These numbers reveal the need for clinical observation of side effects after approval.

The best data on anaphylactic reaction occurrence exist for β-lactam antibiotics. Various studies report between 0.7 and 0.8% allergic reaction occurrence due to β-lactam antibiotics, including anaphylactic reactions. Deadly incidents due to anaphylaxis are reported in 1 in 50,000 to 1 in 100,000 treatment cases. In the U.S., 400–800 deaths a year are caused by anaphylaxis [1]. Retrospective, population-based studies of bullous drug allergies revealed statistically firm epidemiological data on adverse reaction frequency as well as the responsible API. These studies reported an incidence of bullous drug reactions in 1.2/1,000,000 inhabitants a year in France and 0.93/1,000,000 inhabitants per year in Germany [5]. Autoimmune diseases and infections are contributing factors to adverse drug reactions. This is especially true in HIV-infections. Eighty percent of HIV positive patients receiving trimethoprim and sulfamethoxazole (SMX) developed a drug-related allergy, while only 1–3% HIV-negative patients developed an allergy to trimethoprim and SMX [2]. Similarly, 30% of patients suffering from cystic fibrosis develop a sensitization to piperacillin, cefoxidin or ticarcillin, while infectious mononucleosis predisposes patients to develop an amoxicillin allergy.

5.3.3 Etiology and Pathophysiology

5.3.3.1 Immediate Hypersensitivity: Allergic Anaphylaxis

Symptoms of immediate hypersensitivity are urticaria, angioedema, rhinitis, asthma, and in extreme cases, anaphylaxis. The signs and symptoms are mediated by the release of proinflammatory agents from mast cells and basophiles that express highly affinitive receptors to IgE. After the binding of an antigen to at least two neighboring IgE molecules (commonly referred to as “bridging”), inflammation mediators, such as histamine, derivatives of arachidonic acid, and inflammation-promoting proteases and cytokines are released. Drugs are the second most often reason for anaphylaxis (18%) after venom allergy (51%) and occur more often than anaphylaxis by food allergy [6].
recent study drugs were the most often cause of anaphylaxis [7]. API, which frequently provoke these reactions, include contrast media, β-lactam antibiotics, pyrazolones, sulfonamides, anticancer agents such as platin salts, and foreign proteins including those present in extracts for specific subcutaneous hyposensitization [8].

Penicillin and other β-Lactam antibiotics are the best studied drugs which can induce immediate – nonallergic anaphylaxis, as well as hypersensitivity reactions including anaphylaxis by IgE-dependent allergy. In most cases IgE antibodies react to penicilloypenicillin. This forms after the opening of the β-lactam ring, enabling its binding to transport proteins and transformation to an immunologically active form. The transformation to penicilloypenicillin occurs inside and outside the body. Therefore the allergization potential of penicillin also depends upon correct storage of the drug.

Anaphylaxis to contrast media is the most common cause of death by adverse drug reaction of the B-type. Allergic as well as pseudoallergic reactions are precipitated by contrast media [9].

5.3.3.1.1 Pseudoallergic Reactions

Anaphylactic reactions may occur without prior sensitization or participation of allergen-specific IgE. These cases are referred to as pseudoallergic reactions and are caused by toxic or pharmacological effects resulting in the direct release of inflammation mediators from mast cells and basophiles. Examples include:

1. Nonsteroidal anti-inflammatory drugs (NSAID) in the context of NSAID intolerance
2. Antagonists of the angiotensin-converting enzyme (ACE)
3. Angiotensin(AT)-receptor antagonists mediated angioedema
4. Contrast agents
5. Muscle relaxants

Diagnostics of pseudoallergic reactions must always exclude an allergic cause of the reaction, since an allergic reaction requires varying treatment protocols. For instance, a patient with an allergy to diclofenac is sensitized to both diclofenac as well as chemically similar compounds and needs to avoid these drugs. In case of an NSAID intolerance, a heightened risk exists when taking a drug mediating the same pharmacological mechanism irrespective of what the chemical structure is.

With an allergy to single contrast agents or muscle relaxants one must avoid API, which is responsible for the allergy. In case of a contrast agent intolerance without positive cutaneous testing or a positive lymphocyte transformation test (LTT), a premedication with antihistamines and glucocorticoids prior to application of any contrast agent, is usually sufficient to avoid anaphylaxis.

Anaphylactic reactions can also be caused by other factors. For instance, anaphylaxis often occurs after i.v. application of ciclosporine, whereas the same patient tolerates the oral administration of ciclosporine. The anaphylactic reaction is caused by an intolerance to the excipient and histamine-releaser cremaphor, which is not present in the tablet. The excipients used in the tablet are corn oil and gelatin [10–12]

The incidence of anaphylaxis during general anesthesia varies from 1:10,000 to 1:20,000 as reported in an Australian study and 1:13,000 as reported in a French study [13]. The mortality rate is reported as 4–6% [13]. The main causes are neuromuscular blocking agents, use of natural rubber latex, induction agents, opiates, chlorhexidine, and vital dyes used for lymphatic mapping and sentinel lymphnodebiopsies.

5.3.3.1.2 Angioedema Without Urticaria

Drug-induced Angioedema can be caused through three different mechanisms:

1. An IgE-dependent reaction
2. An inhibition of a COX-dependent metabolism pathway of the arachidonic acid, or
3. Activation of the kinine producing system and complement activation

After activation of the kinine system and complement activation, angioedema appears mostly without an accompanying urticaria [14]. In about 1 in 3,000 cases angiotensin-converting-enzyme (ACE)-inhibitors cause pseudoallergic angioedema without urticaria. They inhibit not only the angiotensin system but also inactive bradykinins and substance P, which play an important role in inflammation [15]. Thus, one ACE inhibitor cannot be exchanged for another. In a patient suffering a pseudoallergic reaction to ACE, a medication from a different substance group has to be chosen for further
treatment [16]. It was believed that AT-receptor antagonists would be an alternative to ACE inhibitors. However, even AT-receptor antagonists, although less often, can also cause angioedema. The impact of the kinine system as causing mechanism for angioedema is further corroborated by the fact that patients suffering from hereditary angioneurotic edema (HANE) show similar symptoms after taking ACE inhibitors (Fig. 5.3.1). HANE disease is a contraindication for the therapy with ACE inhibitors [17].

Angioedema without urticaria were also observed after application of sirolimus, a macrolide used as an immune suppressant in organ transplantation. Application of sirolimus allowed reduction and/or discontinuation of calcineurine antagonists in organ transplantation [18].

5.3.3.2 Jarisch-Herxheimer-Reaction

Sudden fever, dyspnea, and hypotension after administration of penicillin in patients suffering from syphilis are known as Jarisch-Herxheimer reaction. New surveys demonstrated that this reaction is accompanied by a sudden, measurable release of TNF-α, IL-6, and IL-8 in serum, known as cytokine release reaction. Anaphylaxis is a differential diagnosis because of a sudden collapse of blood pressure [19]. Similar reactions with a measurable release of TNF-α, IL-6, and IL-8 are also seen after the administration of anti-CD20-antibody rituximab and are related to the concentrations of rituximab. In patients suffering from B-cell-lymphoma the severity of this reaction is furthermore dependent on the actual lymphocyte count [20].

5.3.3.3 Drug-Induced Autoimmune Reactions

The induction of double-stranded (ds) DNA after administration of isoniazid (INH) or hydralazine has long been known [8]. It is caused by slow acetylation of INH. The risk factor that induces ds-DNA after the application of hydralazine is a HLA-locus DRw4. Furthermore, an allergic drug reaction after binding of small molecular substances to proteins or peptides occurs as autoimmune reaction in the affected organism [8].

The administration of TNF-α antagonists, especially infliximab and etanercept may lead to an induction of ds-DNA and some patients showed symptoms of systemic lupus erythematoses. It is speculated, that binding of these drugs to cell-bound TNF-α with subsequent cell death and release of nuclear antigens might induce antibodies to ds-DNA [18]. Similarly, after application of interferon-α (IFN-α) and interleukin-2 (IL-2) induction of thyroid antigens could be detected. The application of IL-2 induced autoimmune thyroiditis [11].

![Fig. 5.3.1 Pathomechanism of Urticaria and Angioedema – the role of ACE-inhibitors and AT1-receptor antagonists](image-url)
5.3.3.4 Delayed-Type Hypersensitivity Reaction and Late-Type Allergy

Hypersensitivity reactions such as purpura or vasculitis occur several hours after administration of a drug. The underlying pathomechanism is mediated by an antigen–antibody complex with either a consecutive complement activation or binding to a cell with a consecutive cytotoxic effect [21, 22]. Quite often these diseases can also be induced by nondrug-related causes. These causes need to be excluded in the diagnostic procedures.

5.3.3.4.1 Allergic Contact Dermatitis

Allergic contact dermatitis (ACD) is considered as a typical example of allergic delayed-type hypersensitivity reaction of the skin. It requires a prior sensitization to a xenobiotic such as a drug. There are several risk factors such as leg ulcers in chronic venous insufficiency, chronic otitis externa, and postoperative wounds. ACD precipitates with pruritus, edematous papules, vesicles, and plaques at the site of contact with the allergen. Although ACD is most often limited to the area of exposure to the antigen, strong reactions or longer exposures to the antigen after sensitization may lead to spreading of more distant sites. Most often involved in this reaction are antibiotics after their topical application. Examples include neomycin, gentamicin, bacitracin, virginiamycin, benzoyl peroxide, chloramphenicol, and clomiphenol [23]. In addition, allergic reactions to contact sensitizers may lead to drug allergy reactions by cross-sensitivity because of similarity in chemistry of the involved compounds. A well-known example is an allergic reaction to sulfonamides or estercaines after sensitization to p-phenylenediamine.

5.3.3.4.2 Maculopapulous Drug-Induced Exanthema

Exanthema is the most common skin disease caused by drugs. It is hypothesized that 60% of all cutaneous drug reactions impose an exanthema. The occasional discovery of a drug causing the reaction by epicutaneous testing or finding of allergen-specific T-cell lymphocytes supports the theory of a late-type allergic reaction as the underlying pathophysiological principle. In some cases patients with a history of drug-related exanthema suffered from a bullous drug eruption when re-exposed. On the contrary, patients with a history of bullous drug eruption develop an exanthema after accidental re-exposure to the causing agent.

5.3.3.4.3 Bullous Allergic Drug Reactions

Besides anaphylaxis, bullous allergic drug reactions are dreaded. Over the last years, epidemiological studies allowed for differentiation of varying forms of drug eruption. The different clinical aspects were accompanied by different prognosis [24]. In particular Stevens-Johnson-Syndrome (SJS) and toxic epidermal necrolysis are severe cutaneous adverse skin reactions (SCAR) characterized by a low incidence but high mortality at least in the latter case.

Fixed Drug Reaction

Until recently, the mechanism of fixed drug reactions was not well understood. A fixed drug reaction is mostly localized acral and imposes as a nummular erythema with a central blister. Drug re-exposure might result in a generalized fixed drug reaction with multiple eruptions on the skin, similar to a toxic epidermal necrolysis [25]. A combination treatment with sulfamethoxazol and trimethoprim is a common cause of a fixed drug reaction. Not only sulfamethoxazol but sometimes trimethoprim can be identified as the causing agent (Fig. 5.3.2), striking the importance of allergologic diagnostics.

Immunohistochemical examination followed by RT-PCR in situ as well as T-cell characterization of isolated cells could reveal that in the lesion of a fixed drug reaction the T-cell population consists of CD8+, CD45RA+, CD11a+ and CD11b+ cells. These cells are effector-memory cells and produce IFN-γ and TNF-α [5]. Interestingly, the same cell population is found in blister fluid of patients suffering from TEN [26]. In patients who were re-exposed to the allergy causing drug, CD4+ T-lymphocytes that produce IL10 and thus feature attributes of Treg cells could be found in addition to the above mentioned T-lymphocytes [27].
Erythema Multiforme-Like Drug Reaction

Many drug-related exanthema are associated with efflorescence similar to erythema multiforme. Drug-related erythema multiforme show an increased tendency to conflueny as compared to herpes infection-related erythema multiforme [28]. If in addition to skin efflorescences mucosal lesions are present, the disease is classified as the major form of erythema multiforme. Whereas this type is most often parainfectious – in particular after a Herpes virus infection – the clinically most frequent distinct type with epidermal detachment of less than 10% of the skin is called SJS.

Stevens-Johnson Syndrome (SJS)

Stevens–Johnson syndrome is primarily a drug-induced disease pattern characterized by erosive mucosal lesions such as stomatitis or conjunctivitis and epidermal detachment (<10%). Other manifestations are fever and involvement of at least one visceral organ, e.g., liver, kidney or gastrointestinal tract [18]. At confluence, the initial purpuriform maculae show a positive Nikolsky’s sign. The incidence rate is 1.2–6/ million [29], the mortality rate is about 1–5%. SJS-TEN describes a transition form to toxic epidermal necrolysis (TEN). About 10–30% of the surface area are effected in SJS-TEN and its mortality rate is between the rate of SJS (1–5%) and TEN (25–35%).

Toxic Epidermal Necrolysis

TEN is one of the most dangerous and often lethal bullous drug reactions and was first described by Lyell in 1956 [30]. Its incidence is 0.4–1.2/million and is more frequently precipitated in women than in man (1.5:1). Further risk factors include slow-acetylator genotypes, HIV-infection, lymphoma, and patients with brain tumors who are undergoing radiotherapy and concomitant therapy with antiepileptics [29]. TEN starts with a mostly painful erythema that develops into blisters, and at least two mucosal areas and more than 30% of body surface area are involved. To better evaluate the prognosis of patients suffering from TEN the SCORTEN – a SJS/TEN specific score – has been employed, evaluating age, malignant diseases, amount of skin surface area involved, tachycardia, and urea, glucose and bicarbonate values as risk factors (Table 5.3.1) [31, 32].

Table 5.3.1 SCORTEN – clinical scoring system to predict the outcome of TEN [8, 29, 46]

<table>
<thead>
<tr>
<th>Clinical–biological parameters</th>
<th>Individual score</th>
<th>SCORTEN (sum of individual scores)</th>
<th>Predicted mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;40</td>
<td>Yes = 1; No = 2</td>
<td>0–1</td>
<td>3.2</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Yes = 1; No = 2</td>
<td>2</td>
<td>12.1</td>
</tr>
<tr>
<td>Tachycardia (&gt;120)</td>
<td>Yes = 1; No = 2</td>
<td>3</td>
<td>35.3</td>
</tr>
<tr>
<td>Initial epidermal detachment &gt;10%</td>
<td>Yes = 1; No = 2</td>
<td>4</td>
<td>58.3</td>
</tr>
<tr>
<td>Serum urea &gt;10 mmol/L</td>
<td>Yes = 1; No = 2</td>
<td>≥5</td>
<td>90</td>
</tr>
<tr>
<td>Serum glucose &gt;14 mmol/L</td>
<td>Yes = 1; No = 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bicarbonate &lt;20 mmol/L</td>
<td>Yes = 1; No = 2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 5.3.2 Cytotoxic drugs such as methotrexat (accidental methotrexat application of 200 mg/week) results in a recall of phototoxic reaction. In this case the patient received first enalapril which is sold as Ena-Hexal® in Germany, and in Turkey she got in a pharmacy Enahexate® which is the trade name for methotrexate in Turkey.
3. Drug Reactions

Drugs which are most often associated with SJS and TEN are shown in Fig. 5.3.3.

Pathophysiological evaluations revealed a central role of cytotoxic T-lymphocytes as the primary cause of necrolysis and subsequent blister formation:

1. Immunohistology of drug-induced bullous reactions such as TEN and Stevens-Johnson syndrome revealed a dermal inflammatory infiltration into the epidermis predominated by CD8+ T-cells [33, 34].

2. Isolation, cloning, and functional characterization of these T-lymphocytes further supported these findings. Hertl et al. were the first, to isolate predominantly CD8+ T-cells from epidermal skin lesions in penicillin-induced bullous drug-reactions [33]. Similarly, mainly CD8+ T-cells could be isolated from test reaction areas of patients after epicutaneous application of penicillin and who had suffered from bullous drug reactions before [35]. These isolated CD8+ T-cells produce cytokines including IL-2 and IFN-γ, but not IL-4 [36].

3. Electronmicroscopy revealed that especially keratinocytes in close proximity to CD8+ lymphocytes showed signs of necrolysis [37].

4. Hertl et al. also showed that T-lymphocytes cloned from lesions that reacted antigen-specific to drugs, such as penicillin, revealed cytotoxic qualities in classic immunological assays against B-lymphocytes. In addition cytotoxic reactions were also seen in target cells, in the case of TEN in keratinocytes [33]. Even in fluid extracted from blisters, CD8+cells can be detected. The isolated CD8+ cells were cytotoxic to EBV-transformed lymphocytes and allogenic HLA-Cw4+ cells in the presence of the causing API [38, 39]. These observations underline the central role of immunologically mediated cytotoxic reactions in the pathophysiology of diseases such as SJS and TEN. Further studies confirmed cytotoxic qualities of epidermal T-lymphocytes; yet, reactions differed in bullous skin reactions, drug exanthema, and AGEP. Thus, in drug exanthema and AGEP CD4+ T-cells dominated besides CD8+cells, whereas in TEN CD8+ cells were the dominant cell type [40]. In drug exanthema, high level of IL-5 could be detected, while in bullous reaction IFN-γ, and in acute generalized eruptive pustulosis (AGEP) IL-8 is overexpressed [9, 41].

Thus far, the initiating mechanism of the apoptosis is still not detected. Several evidences exist which favors an important role for Fas/FasL interaction which leads to the apoptosis of keratinocytes [29]. In particular, in patients suffering from TEN, elevated serum levels of FasL are measurable and this finding coincides with the observation of a highly increased expression of keratinocyte membrane-bound FasL [42]. Additionally it was shown that PBMC-released sFAS Ligand is able to activate keratinocyte Fas-receptors [43]. These findings are supported by analysis of cytokines and their producing cells in the blister fluid. IFN-γ is mainly produced by mononuclear cells and tumor necrosis factor-α (TNF-α), sFASL and IL-10 are produced by activated keratinocytes [44]. However, in drug exanthema perforin- and grancyme B-expressing CD4+ cells dominate the epidermis. Further examination of apoptotic mechanism revealed a perforin- and grancyme-mediated mechanism [44]. These findings suggest that both mechanisms of apoptosis induction are operative in SCAR and may explain controversial results in therapeutic studies with intravenous application of immunoglobulins [29].

Drug-Induced Hypersensitivity Syndrome

Drug reaction with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS) is defined as a drug-related exanthema
with transition into a generalized epidermal necrolysis. Additionally, eosinophilia, lymphadenopathy, liver involvement, fever, and leukocytosis can be found. It is discussed, whether both diseases are different or the same. DRESS is mainly seen after administration of carbamazepine, phenytoin, sulfonamides, and allopurinol [45]. Several distinct features set apart DRESS from other forms of drug-related exanthema and in particular SJS and TEN: DRESS is induced by APIs that have been administered and tolerated over a longer period of time. In these cases the exanthema occurs later than 7–14 days after commencement of therapy. Additionally, cross-reactions between APIs cannot be explained on a molecular basis. Exanthema can reoccur days after discontinuation of treatment [46]. Furthermore, serological tests revealed a titer and DNA increase for HHV6 and CMV 2–3 weeks after outbreak of the exanthema [46].

118 cases in Japan, 63.7% of the cases were caused by antiepileptic drugs and within this group 63% were caused by carbamazepin. Additional substances reported included sulfonamides, mexiletin (antiarrythmic drug), and allopurinol. In 80.5% of all patients the reaction occurred at least 3 weeks after the intake of a drug; in 40% of all cases a reoccurrence was seen and mortality rates were 3.6%. In 83.9%, an increase of immunoglobulin and/or DNA levels for HHV-6 and in 4 out of 118 patients of CMV could be detected [46].

Acute Generalized Eruptive Pustulosis

Likewise, AGEP is a reaction caused by T-lymphocytes, specifically induced by a drug and clinically difficult to distinguish from a pustulous psoriasis. Histology, epicutaneous tests, and LTT help to differentiate the diagnoses [9, 25, 47]. Skin symptoms such as multiple sterile, nonfollicular pinhead sized pustules, oedematous erythema, sometimes accompanied by purpura, blisters, and vesicles arise very rapidly. Systemic symptoms may be fever and leucocytosis. Cloning of T-lymphocytes isolated from AGEP lesions revealed the presence of cytotoxic T-lymphocytes in this disease. Furthermore, an increase in IL-8 expression could be detected in the lesions. This is one explanation for the diagnostic difficulty in distinguishing AGEP from psoriasis [9]. In a recent multinational case-control study (EuroSCAR) 97 AGEP cases were compared with 1,009 controls. Causing drugs with an OR > 5 were the macrolide antibiotic pristinamycine, ampicillin/ amoxicillin, quinolones, (hydroxy)chloroquine, sulphonamides, terbinafine, and diltiazem [48]. Interestingly these drugs differ from the drugs

![Fig. 5.3.4 Drugs which are most often the causes of TEN](image-url)
causing SJS/ TEN (Fig. 5.3.4). Furthermore, IL-8 seems to play a role in the pathophysiology of this disease and drugs which may induce psoriasis such as β-blockers or ACE inhibitors are not among these drugs. The delay between beginning of drug-intake and the onset of reaction differed with regard to the causative drug. In the case of pristinamycin, aminopenicillins, quinolones, and antibacterial sulphonamides the delay was most often 1–2 days, whereas in the case of diltiazem, terbinafine and (hydroxyl)chloroquine it was 7–12 days [48].

### 5.3.3.5 Photoallergic and Phototoxic Reactions

Photoallergic and phototoxic reactions can lead to blisters, which are caused by interaction of an API or its metabolites with UV light. In the case of phototoxicity the drug or its metabolites form radicals under the influence of UV light which enhances the photosensitivity of the tissue. In a photoallergic event, UV light mediates the formation of highly reactive derivatives which bind to proteins in order to make nominative antigens against which sensitization and the formation of specifically reacting T-lymphocytes occur [49]. Photoallergic reactions do occur after topical but only rarely after systemic application of a drug [49]. Clinically, these reactions are denoted by their localization in sun-exposed areas. Especially long-wave UVA light that is preferentially emitted in tanning salons can cause reactions leading to erythrodema. Therefore, a competent medical control for the use of tanning devices should be demanded [50]. Drugs known to cause phototoxic or photoallergic reactions are tetracycline, sulfonamide including sulfoharnylurea drugs, quinolone, and NSAIDs [49]. In the course of development of new drugs, special eyemark is placed on drug interaction with UV light and multiple approaches are made to reveal these drug interactions in preclinical tests [51].

### 5.3.4 Clinical Characteristics and Diagnostics

The aim of diagnostics in allergic and pseudoallergic drug reactions is to identify the causing API and, if possible, the mechanism of action causing the disease. Especially the differentiation of allergic and pseudoallergic reactions is important for risk assessment of future exposure to the drug.

Diagnostics start with an accurate patient history. The most likely cause of anaphylaxis or any other type of drug-induced allergic disease – with the exception of DRESS – is a drug prescribed within 2 weeks prior to start of the symptoms. The patient has usually tolerated the drug for a couple of days. In assessing the anamnestic data a scoring system might be helpful and can be successfully used to rank the most likely

---

**Table 5.3.2** Recommended patch test concentrations [23, 54, 55]

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Concentration</th>
<th>Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neomycin sulfate</td>
<td>20%</td>
<td>Pet</td>
</tr>
<tr>
<td>Gentamicin sulfate</td>
<td>20%</td>
<td>Pet</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>0.1–1%</td>
<td>Aqua</td>
</tr>
<tr>
<td></td>
<td>1%</td>
<td>Pet</td>
</tr>
<tr>
<td></td>
<td>1%</td>
<td>Aqua</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>20%</td>
<td>Pet</td>
</tr>
<tr>
<td></td>
<td>20%</td>
<td>Aqua</td>
</tr>
<tr>
<td>Bacitracin</td>
<td>20%</td>
<td>Pet</td>
</tr>
<tr>
<td>Polymyxin sulfate</td>
<td>3%</td>
<td>Pet</td>
</tr>
<tr>
<td>Pristinamycin</td>
<td>5%</td>
<td>Pet</td>
</tr>
<tr>
<td>Virginiamycin</td>
<td>5%</td>
<td>Pet</td>
</tr>
<tr>
<td></td>
<td>2.5%</td>
<td>Pet</td>
</tr>
<tr>
<td>Penicillin comm prep</td>
<td>1%</td>
<td>Pet</td>
</tr>
<tr>
<td></td>
<td>10,000 IU/gr</td>
<td>Pet</td>
</tr>
<tr>
<td></td>
<td>100,000 IU/mL</td>
<td></td>
</tr>
<tr>
<td>Cloxacillin</td>
<td>Pure</td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Pure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1%</td>
<td>Pet</td>
</tr>
<tr>
<td></td>
<td>5%</td>
<td>Aqua</td>
</tr>
<tr>
<td></td>
<td>5%</td>
<td>Pet</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>1–5%</td>
<td>Aqua</td>
</tr>
<tr>
<td></td>
<td>Pure or scratch test</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.5%</td>
<td>Aqua</td>
</tr>
<tr>
<td></td>
<td>1%</td>
<td>oo</td>
</tr>
</tbody>
</table>

(continued)
involved drugs (Table 5.3.2). The European Network of Drug Allergies (ENDA) has developed a special questionnaire for this purpose [52].

### 5.3.4.1 Skin Tests

For further diagnostics, skin is an important signaling and testing organ. One can utilize prick, intracutaneous, and patch tests. In certain cases, an oral exposure test can be utilized as an additional in vivo testing method. For this purpose the patient should be monitored in an inpatient setting [53].

Skin test plays an important role in the case of allergic reactions to β-Lactam-antibiotica, topical anesthetics, and contrast media. Further testing protocols have been developed for other drugs including sulfonamids, anticonvulsive drugs, muscle relaxants, and NSAID, e.g., diclofenac [12, 54, 55]. Yet only one evaluated testing protocol exists for penicillin. If a positive skin reaction occurs in the skin tests, the patient should be diagnosed with an allergy to the tested substance. On the other hand, a negative skin test result does not exclude an allergization to a drug.

The gold standard of allergy diagnostics is the provocation, but constraints apply to this method as well, since this testing method potentially endangers the patient. Therefore, provocation tests should be performed only at specialized centers after written consent of the patient. Provocation test should under no circumstances be performed after bullous drug reactions like SJS, SJS/TEN, DRESS or TEN, nor in patients with a history of drug-induced hepatitis, nephritis, and hemolytic anemia. Different reactivities have been described for provocation tests and actual application of a drug. Thus, a sensitized patient might not react in a provocation test but at a later exposure to the drug. Furthermore, a positive reaction after provocation does not reveal pathogenesis of the reaction. Guidelines for these tests are provided by the ENDA [56].

A special stance in drug testing is the prick and intracutaneous testing of penicillin allergy. One can test the main nominative allergen benzylpenicilloyl directly or test minor determinants (MDM) like sodiumbenzylpenicillin, benzylpenicilloylacid, and sodiumbenzylpenicilloylato [7, 57]. These tests have been evaluated by different work groups and permit reliable assessments of the risk of an IgE-dependent immediate-type reaction. The negative prediction score has an accuracy of 99% but only, if major- and minor-determinants of penicillin are included in the testing protocol. This means that in a patient with a history of anaphylaxis to penicillin, test doses of, for example, 3–5 mg are tolerated [58]. Furthermore the patch test is an important tool in the diagnosis of sensitization to β-lactam antibiotics, in particular – but not only – if delayed type reactions occurred [54, 55].

Identification of sensitizations to β-lactam antibiotics is important because of different patterns of cross-reactivities between different β-lactam antibiotics depending on the underlying sensitization. Thus, patients with drug reactions to ampicillin might be sensitized to amino groups in the subchains of β-lactam antibiotics. These patients will be able to use Penicillin G or V without any risk of drug reaction. On the other hand, patients with a sensitization to the main allergen penicilloyl will have cross-reactions between all β-lactam antibiotics [59, 60]. Of high importance is the

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Concentration</th>
<th>Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalexin</td>
<td>1% Pure</td>
<td>oo</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>1% 10% Pet</td>
<td></td>
</tr>
<tr>
<td>Sulfate</td>
<td>2%, 25% Pet</td>
<td></td>
</tr>
<tr>
<td>Stearate</td>
<td>1% Pet</td>
<td></td>
</tr>
<tr>
<td>Benzoyl peroxide</td>
<td>1% Pet</td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>5% Pet</td>
<td></td>
</tr>
<tr>
<td>Clindamycin hydrochloride</td>
<td>1% Aqua</td>
<td></td>
</tr>
<tr>
<td>Clioquinol</td>
<td>5% Pet</td>
<td></td>
</tr>
<tr>
<td>Fusidic acid sodium salt</td>
<td>2%, 2% Pet, Aqua</td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td>2% Pet</td>
<td></td>
</tr>
<tr>
<td>Mupirocin</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Nitrofurazone</td>
<td>1% Pet</td>
<td></td>
</tr>
<tr>
<td>Rifamycinc</td>
<td>0.5% 0.5–2.5% Pet</td>
<td></td>
</tr>
<tr>
<td>Oxytetracycline</td>
<td>3%, 10% Pet</td>
<td></td>
</tr>
</tbody>
</table>
evaluation of cross-reaction to cephalosporine. The risk to develop a cross-reactivity is dependent on the generation of cephalosporine. First generation cephalosporines show cross-reactivity in 5–16.5% while second generation cephalosporines (e.g., cefazoline) have 4% cross-reactivity. For third and fourth generation cephalosporines, the risk of cross-reactivity is stated with 1–3% [18]. It is still unclear, whether a true cross-reactivity between penicillin derivatives and cephalosporines exists, or if patients allergic to antibiotics have a higher risk of developing allergies to other drugs. In either case, the risk of developing an allergic reaction to cephalosporine is higher in patients with an allergy to penicillin than in those without an allergy [61]. The high negative prognostic value of the penicillin skin test is applicable to cephalosporine in case of a negative history of drug eruption due to cephalosporine [61]. Skin tests with 2 mg/mL cephalosporine seem to have a high negative prognostic value in case of a positive patient history of drug reaction to cephalosporine [62]. Romano et al. demonstrated that patients showing negative reactions to cephalosporine in skin tests do not have the risk of allergic drug reaction after administration of cephalosporine. Therefore, it is strongly recommended for patients with a history of penicillin allergy to perform skin tests to investigate a potential cephalosporine intolerance prior to drug administration. Therefore, prick and intracutaneous skin tests of β-lactam antibiotics should include the prevalent nominative antigen penicilloylpolylysine, minor determinants as well as bencylpenicillin, ampicillin, amoxicillin, piperacillin and different cephalosporines like cephalotin, cefamandol, cefuroxim, ceftazidin, cefotaxim, and ceptriaxon. In a study employing this testing system, Romano et al. detected a positive skin test reaction to penicillin or its derivatives in 128 patients. Forty-four of these 128 (10.9%) patients had a positive skin test to a cephalosporine. In nine of these 14 patients the positive reaction was to cefamandol. Hundred and one of the 114 patients with a negative cefaloridine skin test underwent provocation with cephalosporine – none of the patients showed an allergic reaction to cephalosporine. These findings and the fact that more than 10% of patients with sensitization to penicillin showed cross-reactivity to cephalosporine led the author to recommend the administration of cephalosporine to patients allergic to penicillin only after prior skin testing [62].

In an additional study, Romano et al. demonstrated that patients with anaphylaxis to cephalosporine without a known hypersensitivity to penicillin reacted primarily to cefuroxim, cefotaxim, and ceftriaxon [63]. Recently an anaphylaxis to cephalozine was observed during surgery. This allergy could be confirmed in the skin test, a basophile activation test, and by a CAST (cellular antigen stimulation test) -assay. Cross-reactivity occurred against Cefotiam, Cefuroxim, and Cefuroximaxetile, whereas no sensitization was observed against penicillin, amoxicillin, and ceftriaxone, which belong to the cephalosprines of the third generation. This could be confirmed in a challenge test [64].

Another problem is the cross-reactivity between penicillin and carbapenem derivatives – in particular of imipenem and meropenem, with a reported high cross-reactivity of 47.7% [65]. However, a recent study including 112 cases of penicillin allergy showed cross-reactivity to meropenem. Similar data was reported for imipenem/cilastatin (1/104) as well as for meropenem (tested with 1 mg meropenem/ml saline) in children (1/108). These data were confirmed by negative skin test result in the challenge test [65, 66].

If an incompatibility to topical anesthetics is suspected, diagnostics should include a patch test (sensitizations to substances substituted para to the NH₂ group), prick- and intracutaneous tests with a dilution of 1:100. A provocation test should be performed by subcutaneous application of the topical anesthetic. To verify the results placebo controlled tests like reverse placebo provocation have been suggested [67]. In a reverse placebo test, the test substance is noticeable to the patient as placebo and vice versa. The following day the patient learns about the tested substances and the test is repeated as an open label test [67].

Contrast agents are the main cause of death caused by allergic or pseudoallergic drug reactions. Anaphylaxis to contrast agents is seen in 23% of all applications [68]. Hypertone as well as hyperosmolar properties of the contrast media are accused to cause anaphylactic reactions. The introduction of nonionic and isotonic, dimer contrast agents have reduced the amount of side effects seen. Yet, anaphylactic reactions have also been described to these new substances, and are mainly seen as late-type reactions after hours and up to 7 days after application (see Table 5.3.3) [69]. Most of these anaphylactic reactions are pseudoallergic, caused by an increased release of histamine by contrast media. However, some patients, especially after late-type reactions, show a positive
H. F. Merk and D. H. Obrigkeit

Table 5.3.3  Suggested concentrations for drug skin tests [13, 113]

<table>
<thead>
<tr>
<th>Medication</th>
<th>Concentration (mg/mL)</th>
<th>Intradermal skin test</th>
<th>Skin prick test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Succinylcholine</td>
<td>0.1</td>
<td>0.05</td>
<td>0.02</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>0.2</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>0.4</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Alcuronium</td>
<td>0.05</td>
<td>0.005</td>
<td>–</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>0.003</td>
<td>0.001</td>
<td>0.0003</td>
</tr>
<tr>
<td>Gallamine</td>
<td>0.2</td>
<td>0.04</td>
<td>–</td>
</tr>
<tr>
<td>Metocurine</td>
<td>–</td>
<td>–</td>
<td>0.002</td>
</tr>
<tr>
<td>Methohexital</td>
<td>–</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Protamine</td>
<td>–</td>
<td>0.001</td>
<td>–</td>
</tr>
<tr>
<td>Thiopental</td>
<td>–</td>
<td>0.25</td>
<td>0.20</td>
</tr>
<tr>
<td>Thiamylal</td>
<td>–</td>
<td>0.01</td>
<td>–</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>0.1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>0.002</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Atracurium</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Decamethonium</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Codeine</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Morphine</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pethidine</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Papaveretum</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Diazepam</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Midazolam</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Neostigmine</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Atropine</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Benzylkonium</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Droperidol</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Propofol</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Dextran 70</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Gelofusine</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Haemaccel</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Positive intradermal skin test result: wheal greater than 8 mm; positive skin prick test result: wheal greater than 4 mm
reaction in patch test and LTT, suggesting an allergic reaction in these patients (Fig. 5.3.5) [70]. Usually, late-type reactions are not severe or life threatening but manifest as itching with or without urticaria and only rarely show a more severe progression. By reason of these observations allergy testing procedure to identify intolerance reactions to contrast agents are suggested and listed in Table 5.3.4.

### 5.3.4.2 In Vitro Test

Pathophysiological factors of a drug reaction might be revealed by in vitro tests. These tests have the advantage of not endangering the patient’s life. There are serological and cell-based tests available. Serological tests are usually performed at central laboratories, and are easy to evaluate in epidemiological studies. Cell-based tests require the presence of a patient at the testing site or elaborate logistics to ensure fast processing of blood or tissue samples.

### 5.3.4.3 Serological Testing Systems

The most important serological test is the determination of specific IgE after anaphylaxis. Routinely this is performed in penicillin sensitization only. Specific IgE to latex, chlorhexidine or muscle relaxants can be measured if the patient reports a specific history during general anesthesia. Propositions, to identify specific IgE to acetylsalicylic acid, codeine, phenazon, tartrazin or contrast agents are not subject to reliable allergy diagnostics.

In addition, measurements of tryptase levels in serum up to 2 h after severe anaphylaxis are used to

---

**Table 5.3.4** HLA-associations as a risk factor for adverse drug reactions (ADR) (according to [108])

<table>
<thead>
<tr>
<th>Alleles oder haplotypes</th>
<th>Drugs</th>
<th>HLA associated ADR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-B*1502</td>
<td>Carbamazepine</td>
<td>Stevens-Johnson-Syndrome</td>
</tr>
<tr>
<td>HLA-DRB1<em>1501/HLA-DQB1</em>0602/HLA-DRB5*0101</td>
<td>Amoxicillin-Clavulanacid</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>HLA-DQ7</td>
<td>Pyrazolone</td>
<td>Pyrazolon-hypersensitivity</td>
</tr>
<tr>
<td>HLA-A29/HLA-B12/HLA-DR7</td>
<td>Sulfonamide</td>
<td>TEN</td>
</tr>
<tr>
<td>HLA-B38/HLA-DR4,HLA-DQ3/HLA-Cw<em>7/HLA-DQB</em>0502/HLA-DRB<em>0101/HLA-DRB3</em>0202</td>
<td>Clozapine</td>
<td>Agranulocytosis</td>
</tr>
<tr>
<td>HLA-B*5701/HLA-DR7/HLA-DQ3</td>
<td>Abacavir</td>
<td>Abacavir-hypersensitivity</td>
</tr>
<tr>
<td>HLA-DR4</td>
<td>Hydralazine</td>
<td>Drug-induced SLE</td>
</tr>
<tr>
<td>HLA-B*5801</td>
<td>Allupurinol</td>
<td>TEN</td>
</tr>
</tbody>
</table>
H. F. Merk and D. H. Obrigkeit
diagnose involvement of basophiles in the reaction. Thus, anaphylaxis can be confirmed. Furthermore the results indicate a mastocytosis that might explain the severity of the allergic reaction [71].

5.3.4.4 Cellular Testing Systems

Cell-based allergy diagnostics are performed with basophiles and T-lymphocytes.

5.3.4.4.1 Basophile Activation Test

This test determines the reactivity of basophiles after incubation with the suspected drug. Reactions are evaluated by measurement of released histamine (histamine-release test), the released cysteinyl-leukotrienes after the addition of IL-3 (CAST-ELISA) as well as the fluorescent detection by flow cytometry of CD63 or CD203c in activated basophiles. This assay has lately been described as a promising tool in the diagnosis of allergies to muscle relaxants and β-lactam antibodies [3, 72]. In combination with a CAST-Elisa, the sensitivity of diagnostics in NSAID intolerance could be improved [3].

5.3.4.5 Lymphocyte Transformation Test (LTT)

In vitro tests of basophiles only detect immediate-type allergic or pseudoallergic reaction. T-lymphocytes on the other hand play a central role in immediate as well as late-type immune responses. The LTT has been widely employed to identify T-cell related responses to drugs in vitro in sensitized patients. In short, lymphocytes of sensitized patients and healthy controls are incubated with the drug in question. Drug-specific T-cell proliferation is measured after 5–7 days by H3-thymidin marking of the cells. In the past, the LTT has been helpful in individual cases to objectify T-cell reactions to an API, e.g., β-Lactam antibiotics, anticonvulsives or sulfonamides [73–75]. A high quality of results requires meticulous planning, including the controls. It is recommended to perform a LTT within 3 months of the allergic reaction. Due to a low frequency of drug-specific T-lymphocytes in peripheral blood, the measurable drug-induced T-cell proliferation is low. This complicates the differentiation of significant positive and negative results [73]. These findings are supported by Roujeau et al. Their study revealed that a few months after a TEN, no drug-specific T-cell responses could be determined, although in isolated cases T-cell-specific reactions to APIs could be determined for years [76]. Despite these difficulties, the LTT is more specific and sensitive towards allergic reactions to β-lactam antibiotics and topical anesthetics, than skin tests [77–79]. Therefore in selected cases, this elaborate test might be expedient and should be performed in experienced laboratories. Improvements to this test have recently been introduced. These new methods use not only the API in question, but also its metabolites to induce proliferation. Additionally, not only proliferation, but also expression of surface activation markers such as CD69 or antigen-specific cytokine profiles are being measured [41, 80]. A recently described carbocyanine succinimolylester dilution assay allows to measure – similar to the determination of CD69 expression – activation or proliferation of the lymphocytes as well as the cytokine production [81].

5.3.4.6 Allergy Card

At the end of every allergy diagnostic, the patient should receive an allergy card. The card should not only indicate the suspected API, but also the basis of diagnostics (patient history, specific IgE, positive skin test reaction or re-exposure) and, if checked, an alternative API to use.

5.3.5 Role of Drug Metabolism

5.3.6 General Therapeutic Outline

The therapy of drug allergic or nonallergic reactions such as anaphylaxis, purpura, vasculitis, etc. does not differ from the treatment of these reactions if they are induced by other causes. Maculopapulous drug-induced exanthema, AGEP, fixed drug reaction or contact dermatitis is normally treated by topical or systemically
5.3 Drug Reactions

applied glucocorticoids. Special aspects do exist for bullous drug reactions, such as SJS and TEN. In some cases also prevention by pretreatment with antiallergic drugs or desensitization are performed and will be discussed in the session of current established therapies.

5.3.7 Current Established Therapies

Optimal treatment strategy in the case of anaphylaxis depends upon the severity of the reaction. In several unavoidable risk situations pretreatment with antiallergic drugs or desensitization are recommended.

For a patient with a history of anaphylaxis after treatment with contrast medium or muscle relaxants, and if an allergic reaction could be ruled out by skin test or LTT, a prophylactic treatment with H1 and H2-antihistamines and glucocorticoids prior to re-exposure with the causing API is recommended. Furthermore, a low-molar contrast agent should be favored [68]. Desensitization is performed more often in the US than in Europe. In Europe treatment with a substitute API is favored in nearly all situations [82, 83]. In prophylaxis of allergic drug reactions, the use of omalizumab to initiate penicillin hyposensitization has been described recently [84]. Indications for this desensitization approach are seen in patients suffering from cystic fibrosis as well as for cisplatin allergizations [83, 85]. The underlying mechanism of this form of desensitization is not yet known. It seems to be different from classical forms of hyposensitization used in rhinitis allergic, since tolerance seems to be given only for the duration of interval-free treatment [85].

Standard treatment options for allergic drug exanthema and bullous drug reactions are glucocorticoids. The use of steroids in the treatment of TEN on the other hand is discussed controversially, since TEN may occur under high-dose treatment with glucocorticoids [38]. However, in this extraordinarily severe form of epidermal drug reaction, positive treatment results with glucocorticoids are seen only during the first few days after onset of the disease; later glucocorticoid treatment increases the risk for sepsis. Other studies revealed a fast effectiveness of low-dose cyclophosphamid treatment during the first few days after the onset of TEN [86]. Furthermore, plasmapheresis seems to be beneficial in TEN, if the causing API is eliminated faster this way [87].

The evidence of involvement of FasL in the pathogenesis of TEN led to the experimental use of IVIG, utilizing the potential anti-FAS activity of immunoglobulines. It is recommended to start early in the disease with intravenous application of immunoglobulin at a concentration of 0.2–0.75 g/kg body weight and treatment should continue for 4 days. Results on therapeutic effects from different groups were not consistent, which is most probably due to different anti-Fas properties of the used products or little relevance of the Fas/FasL pathway in apoptosis [18, 42]. Patients suffering from EM major caused by hypersensitivity to contrast medium were treated with IVIG prior to re-exposure to contrast medium. The patients received 200 mg/kg/day (Gammar-P, Aventis) in addition to the prophylactic treatment with 60 mg prednisone 1 day prior to treatment, on the day of treatment as well as the following 2 days [88]. The prophylactic administration of IVIG helped prevent an allergic reaction at re-exposure.

A multifaceted therapeutic approach has been proposed consisting of elimination of residual drug, immunosuppression, antiapoptotic strategies, and aggressive supportive care. The elimination of the drug can be enhanced by plasmapheresis and N-acetylcysteine (2 g/6 h), immunosuppression has been performed with cyclosporine (3–4 mg/kg/day) and cyclophosphamide (100–300 mg/day), whereas the application of glucocorticoids is controversial and it may even increase the mortality [29]. A controlled study with thalidomide had to be interrupted because of a higher mortality rate in the treatment group [89]. Several studies were performed with IVIG, most, but not all, of these studies showed a benefit, and these studies were not conducted in a randomized, controlled fashion. The largest study was done in 48 patients with a mean total dose of 2.7 g/kg (doses ranging from 0.65 to 5.8 g/kg divided over 1–5 days). The therapy was introduced on an average of 7.3 days after onset of the disease and demonstrated a rapid cessation of skin and mucosal detachment. It is important to take into consideration that there are large batch to batch variability with regard to the anti-Fas activity of IVIG and some batches may lack activity completely, which may explain different results in different studies [29].

Treatment of TEN with ciclosporine in a dose of 3–5 mg/kg/day i.v. for 8–24 days resulted in a fast effect on blister formation and healing, yet it may put a patient with a tendency to develop sepsis at risk. It is
difficult to evaluate the effect of ciclosporine as the causing API of sepsis in these patients or perform controlled studies to investigate this effect [18]. The experimental application of thalidomid or TNF-α-antagonists led to controversial results and these substances should not be applied until the main mechanism of apoptosis in TEN is found [18].

Especially in allergic and pseudoallergic drug reactions the diagnostic steps to find the etiological drug is an important element of the therapeutic approach. Avoidance of a drug is the only way to prevent the reoccurrence of an anaphylaxis.

5.3.8 Experimental Approaches

Studies about the role of drug metabolism in allergic reactions to small-molecular weight compounds as well as how they are recognized by T-lymphocytes were a major focus in research in order to improve our understanding of allergic drug reactions as well as to improve in vitro diagnostic assays.

In contrast to the above-mentioned examples of β-lactam antibiotics, most drugs are metabolized by the body. In the first phase of metabolism, oxidative reactions change an API into a highly reactive chemical substance with a high affinity to proteins and peptides. These reactions are mainly mediated through cytochrome P450-isoenzymes that are primarily located in the liver but are also present in extra-hepatic organs, including the skin. [89, 90]. This metabolic pathway emphasizes the hypothesis by Landsteiner that small molecular haptenes require to become bound to peptides or proteins in order to become antigenic. Analysis of anticonvulsives – phenytoin, carbamazepine, and lamotrigine – and sulfonamides generated evidence for the importance of oxidative metabolism in developing an API sensitization. Important enzymes include the above-mentioned cytochrome P450-isoenzyme.

SMX-specific T-cells in a patient with a bullous exanthema revealed a significant proliferation of SMX and autologous irradiated lymphocytes as antigen-presenting cells in vitro. Even after addition of SMX-modified murine liver microsomes that were rich in drug metabolizing cytochrome P450-enzymes, T-cells proliferated. The induction was shown despite the fact that oxidized sulfonamides and their metabolites revealed an immunosuppressive activity in T-cells [91–93]. SMX is acetylated to N4-acetyl-SMX and metabolized by cytochrome P450 2C6 to 5-hydroxy-SMX or a reactive hydroxylamine [17, 94]. The hydroxylamine metabolite can be eliminated by glutathion-synthetase or, after spontaneous oxidation, formed into Nitroso-SMX that becomes immunogenic by binding to macromolecules. Further studies revealed the presence of antibodies against protein-sulfonamide-compounds in patients with late-type sensitizations to sulfonamides [95, 96]. Glucose-regulating protein 78 (grp78) and the proteindisulfide-isomerase could be identified as the binding structure in the endoplasmatic reticulum [95]. Although these studies did not reveal the pathophysiological role of these antibodies as cause or epiphenomenon of the reaction, they underline the importance of the oxidative, cytochrome P450-dependent metabolism in sensitization of a patient.

Anticonvulsives such as phenytoin, carbamazepine, lamotrigine or benzodiazepam are metabolized to highly reactive arenoxide metabolites by cytochrome P450-dependent enzymes and can be detoxified by epoxid hydrolases. Alternatively, cytotoxic intermediate metabolites can bind to a protein and therefore can be immunogenic [97]. A lymphocyte-toxicity assay has been developed to help determine a phenytoin sensitization in vitro. In addition, the lymphocyte reaction to phenytoin and carbamazepine could be improved after addition of liver microsomes with cytochrome P450-activity to LTT [74, 98]. It was also shown that skin expresses cytochrome-P450 isoenzymes capable of metabolizing carbamazepine into reactive metabolites that bind covalently to proteins [89]. Finally, antibodies to cytochrome P450 3A4, the enzyme metabolizing anticonvulsives, could be detected in patients with sensitization to anticonvulsives. T-cell clones of these sensitized patients reacted to metabolites of carbamazepine [99]. The role of such antibodies in diagnostics needs further evaluation.

Benzodiazepam allergies are characterized by a cytochrome P450-dependent sensitization as well as an increased T-lymphocyte proliferation and an increased IL-5 expression and release [41]. These findings are in accord with findings in phenytoin sensitization. In these cases, a polyclonal stimulation was detected in LTT; on a molecular level, cell activation required processing of phenytoin [100].

To diagnose sensitizations to nevirapine, an animal model has been developed [101]. The model revealed
that the sensitization was primarily induced by a cytochrome P450-dependent 12-hydroxy-metabolite of nevirapine. Interestingly, the API, but not the metabolite was cognized by T-cell clones that could be isolated after the sensitization. This demonstrates that a sensitization might be caused by metabolites of an API but not be recognized by T-lymphocytes or vice versa: APIs that are recognized by sensitized T-cells do not necessarily reveal the conditions leading to the sensitization [101].

Studies on T-cell clones isolated from patients sensitized to an API revealed that the API in question was able to activate sensitized T-lymphocytes directly. These results refute earlier findings that oxidative metabolism of an API is necessary to develop antigens. This type of reaction is found in sensitization to topical anesthetics, anticonvulsives, sulfonamides, and in our own studies, in contact allergies such as p-phenylendiamin [4, 102]. These observations suggested the i-p principle – a direct T-lymphocyte reaction to such substances without prior processing by an antigen-presenting cell [4]. One has to bear in mind that most T-cell clones examined reacted to the API as well as to its metabolite(s). In the murine system, allergizations were inducible only with oxidized metabolites [103–105]. Furthermore, especially the model for nevirapine allergization showed that metabolites other than those detected by T-cells might play a role. These findings underline that the i-p principle does not sufficiently explain antigen processing and presentation. Metabolization seems to be at least a necessary danger signal in this phase of sensitization. Despite these drawbacks, the i-p-principle can still be applied to LTT diagnostics as demonstrated for sulfonamides or p-phenylendiamines in contact eczema because in these assays T-lymphocytes of already sensitized individuals are investigated Taken together, the role of drug metabolism and the i-p-principle result in at least three models of how T-lymphocytes recognize the drug against which they are sensitized (Fig. 5.3.6) [102].

Currently, three developments are under investigation to explain pathophysiology of allergic drug reactions on the skin. These approaches might influence our diagnostic and therapeutic abilities:

1. Establishment of animal models enable examination of the primary sensitization phase – as applied in diagnostics of sensitized patients – and also comparison of the secondary inducers of the reaction as well as analysis of sequences of allergic reaction [106]. In such models the role of e.g., regulating Treg cells in allergic drug reactions or autoimmune drug reactions could be demonstrated and the role of toll-like-receptors could be demonstrated for the first time [107]. Furthermore, these models allow the control of therapeutic concepts, like in TEN [108].

2. The ability to test API in human antigen-presenting dendritic cells creates the capability to test immunogenicity of small molecular substances. The metabolism of these substances can be altered by establishing artificial metabolizing systems [109].

3. Recent pharmacogenetic studies have revealed individual risk factors such as HLA-association, as shown in Table 5 [110]. A better assessment of risk factors would enable development of improved individual therapy and therefore contribute to an increase in drug safety. These studies might also increase our knowledge about pathophysiological mechanisms. Thus, the antiviral drugs abacavir and nevirapin cause drug exanthema or bullous drug eruptions in up to 10% of the patients. Patients reacting to abacavir had a strong association to the allele HLA-B*5701, patients who reacted to nevirapine were correlated to HLA-DRB1*0101 and a comparably high CD4+ T cell fraction. The reaction to abacavir can be detected by a patch test and shows a 100% correlation to HLA-B*5701 [111]. It was found that carbamazepine associates with the allele HLA-B*1502. The gene encoding for heat shock protein HSP70 is located in close proximity to this allele and is therefore a candidate for polymorphism. This polymorphism shows a
varying association with development of DRESS to carbamazepine (Table 5.3.4). Interestingly, HSP70 is the protein with the highest affinity to carbamazepine and therefore most likely to develop the antigen.

5.3.9 Complications to Avoid

The worst complication in patients with a history of drug allergy is the accidental reapplication of the drug or a chemically related compound. In order to prevent this, it is most important to give patients with the history of drug allergy an allergy card in which the history (kind of reaction) and the result of diagnostic procedures (skin tests, in vitro tests) as well as possible alternative drugs are mentioned [101].

5.3.11 Global Variations (For the Therapy)

There are major differences with regard to diagnostic procedures in Europe and Japan on one side and the USA on the other. One example is allergic reactions to β-lactam-antibiotics. In the USA skin tests are recommended only for immediate-type reactions but not for nonimmediate-type drug allergy [82]. In Europe skin tests as well as in vitro assays such as the LTT are recommended in nonimmediate reactions to β-lactam-antibiotics [7]. In the USA drug desensitization is more commonly performed than in Europe. This is especially true for desensitization of β-lactam-antibiotics and chemotherapeutic agents. This also results in different recommendations e.g., for the treatment of syphilis with β-lactam-antibiotics and the application of platin salts in oncology [83, 112].

References


5.3 Drug Reactions


Further Reading


Hypersensitivity Syndrome Reaction

5.4

Sandra R. Knowles and Neil H. Shear

5.4.1 Clinical Characteristics and Diagnosis

HSR is characterized by a triad of fever, skin eruption, and internal organ involvement. This syndrome has been well described for a number of drugs, including anticonvulsants, sulfonamide antimicrobials, lamotrigine, dapsone, allopurinol, and minocycline. Although this reaction has been estimated to occur between 1 in 1,000 and 1 in 10,000 anticonvulsant and sulfonamide antibiotic exposures, its true incidence is unknown because of variable presentation and inaccurate reporting. For anticonvulsants, HSR is more frequently associated with phenytoin (2.3–4.5 cases per 10,000) exposures and carbamazepine (1.0–4.1 cases per 10,000) [1]. HSR occurs most frequently on first exposure to the drug, with initial symptoms starting 2–12 weeks after exposure. The timing varies with each drug. For sulfonamide antimicrobials, the delay of onset is closer to 2 weeks, and for carbamazepine, it is 3 weeks. In patients with a history of HSR, re-exposure to the offending agent may cause the development of symptoms within 1 day. HSR is not related to dose or serum concentration of the drug.

A mild to high fever ranging from 38 to 40°C and malaise, which can be accompanied by pharyngitis and cervical lymphadenopathy, are the presenting symptoms in most patients. Atypical lymphocytosis with a subsequent prominent eosinophilia may occur during the initial phases of the reaction in many patients [1]. A generalized exanthem occurs in approximately 85% of patients and usually occurs simultaneously with the onset of fever or shortly after. Skin manifestations can range from an exanthematous eruption to more serious eruptions such as exfoliative dermatitis [3]. Conjunctivitis may also be present in some patients [3]. In patients with

Key Features

- Characterized by a triad: fever, skin rash, and internal organ involvement
- Most commonly associated medications include aromatic anticonvulsants (e.g., phenytoin, phenobarbital, carbamazepine, Oxcarbazepine), lamotrigine, abacavir, sulfonamide antimicrobial drugs, dapsone, allopurinol, and minocycline
- Usually occurs on first exposure to drug with initial symptoms starting 2–6 weeks after exposure
- Monitoring of patients include liver transaminases, bilirubin, complete blood count, urinalysis, serum creatinine, and any other test specific to internal organ involvement (e.g., chest X-ray for respiratory symptoms)
- If symptoms are severe or organ failure is pending, prednisone (1–2 mg/kg/day) can be used. Topical corticosteroids and antihistamines are used for symptomatic relief.

Synonyms

DIHS    Drug-induced hypersensitivity syndrome
DRESS   Drug rash (reaction) with eosinophilia and systemic symptoms (signs)
anticonvulsant-induced HSR, facial edema may be present [4]. Other features may include exudative tonsillitis, pharyngitis, mouth ulcers, flu-like symptoms, myopathy, and disseminated intravascular coagulation. Liver abnormalities, presenting as elevated transaminases, alkaline phosphatase, prothrombin time, and bilirubin are present in approximately 50% of patients; in some patients, the development of severe hepatitis with jaundice may occur [5]. Other organs such as the kidney (interstitial nephritis, vasculitis), central nervous system (encephalitis, aseptic meningitis), or the lungs (interstitial pneumonitis, respiratory distress syndrome, vasculitis) may less commonly be involved. A small subgroup of patients may become hypothyroid as part of an autoimmune thyroiditis within 2 months of initiation of symptoms [6]. This is characterized by a low thyroid level, an elevated level of thyroid-stimulating hormone, and autoantibodies, including antimicrosomal antibodies. Colitis, with a mixed interstitial inflammatory infiltrate, can present with hematochezia and abdominal pain. This is rare, so may be missed, and can be a cause of death due to colonic rupture and sepsis.

A review of 216 patients with symptoms and signs consistent with HSR was recently published [7]. Reports were analyzed retrospectively from the French Pharmacovigilance database over a period of 15 years. Forty percent of cases were attributed to anticonvulsants (namely carbamazepine, phenytoin, phenobarbital, and lamotrigine), 10% to allopurinol, 8% to minocycline, 10% to nevirapine and 32% to abacavir. Skin lesions typified by a diffuse maculopapular inflammatory rash and erythroderma. Less frequently, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS) or erythema multiforme were reported. Fever was present in 23–100% of cases. Eosinophilia was the most frequent hematological abnormality, present in more than 50% of cases. Similarly, liver abnormalities were the most frequently observed systemic symptoms (more than 60%). Renal dysfunction was observed in 43% of allopurinol cases, whereas with other drugs it was rarely reported.

### 5.4.2 Etiology and Pathophysiology

Many drugs associated with severe idiosyncratic drug reactions are metabolized by the body to form reactive, or toxic, drug products [8]. These reactive products comprise only a small proportion of a drug’s metabolites and are usually rapidly detoxified. However, in patients with HSS, TEN or SJS, one of these metabolites may act as a hapten and initiate an immune response, stimulate apoptosis, or cause cell necrosis directly [9, 10].

**Aromatic Anticonvulsants:** HSR has been associated with the aromatic anticonvulsants, namely phenytoin, phenobarbital, and carbamazepine [11]. It has been suggested that the formation of toxic metabolites by phenytoin, carbamazepine, and phenobarbital may play a pivotal role in the development of HSR [10]. Phenytoin, carbamazepine, and phenobarbital are metabolized by various cytochrome P-450 (CYP) enzymes to chemically reactive metabolites, although the specific metabolite is unknown. For example, a reactive metabolite formed with carbamazepine includes carbamazepine-2,3-epoxide [12]. This metabolite is thought to be detoxified by epoxide hydroxylases; however, if detoxification is defective, the toxic metabolite may act as a hapten and initiate an immunoresponse, causing cell necrosis directly or indirectly via pathways leading to apoptosis. Recent work suggests that there is an association between Human Herpesvirus 6 (HHV-6) infection (either initial infection or reactivation) and severe hypersensitivity syndrome [13, 14]. Viral infections may act as, or generate the production of, danger signals leading to damaging immune responses to drugs, rather than immune tolerance [15].

No association between HLA-B*1502 allele and antiepileptic-induced HSR was found in a recent study [16]. HLA-B*1502 was associated with severe cutaneous reactions, namely SJS and TEN, induced by aromatic anticonvulsants (carbamazepine, phenytoin and lamotrigine), but was not associated with maculopapular exanthema or HSR.

Approximately, 70–75% of patients who develop anticonvulsant HSR in response to one aromatic anticonvulsant show cross-reactivity to the other aromatic anticonvulsants. In addition, in vitro testing shows that there is a familial occurrence of HSR due to anticonvulsants [10]. Siblings of patients who developed HSR may have up to 25% probability of experiencing a similar reaction when exposed to a drug of the same class. Thus, counseling of family members and disclosure of risk is essential.

Although lamotrigine is not an aromatic anticonvulsant, several reports have documented a hypersensitivity syndrome associated with its use as well [17]. Data
demonstrate that a reactive metabolite may also be important in the pathogenesis of lamotrigine hypersensitivity syndrome [18]. Lamotrigine was not observed to cross-react with the other anticonvulsants.

**Sulphonamide Antimicrobials:** Sulphonamide antibiotics have also been reported to cause HSR in susceptible individuals [19]. The primary metabolic pathway for sulphonamides involves acetylation to a nontoxic metabolite, followed by renal excretion. An alternative metabolic pathway, quantitatively more important in slow acetylators, involves the CYP enzymes [20]. These enzymes can transform the parent compound to reactive metabolites, namely hydroxylamines and nitroso compounds that produce cytotoxicity independent of preformed drug-specific antibody [21]. In most individuals, detoxification of the metabolite occurs. However, in patients who are unable to detoxify this metabolite (e.g., glutathione deficient), HSR may develop [9]. The detoxification defect is present in 2% of the population, but only 1 in 10,000 people manifest symptoms of HSR. However, the patient’s siblings and other first-degree relatives are at an increased risk (perhaps 1 in 4) of having a similar defect. Other aromatic amines, such as procainamide, dapsone, and acetobutolol, are metabolized to similar compounds. Clinicians generally recommend avoidance of these drugs in patients who develop symptoms compatible with a sulphonamide HSR because of the potential for cross-reactivity. However, cross-reactivity with sulphonamides should not occur with related drugs that are not aromatic amines (e.g., sulfonyleucaas, thiazone diuretics, furosemide, acetazolamide) [22]. Similar to HSR due to anticonvulsants and allopurinol, there is some evidence to suggest that reactivation of a latent HHV-6 infection may be linked to the development of sulphonamide-induced HSR [23].

**Minocycline:** Minocycline has also been associated with minocycline [24], usually occurring 2–4 weeks after therapy is started. The pathogenesis of minocycline-induced HSR is unknown; however, minocycline metabolism may generate an iminquinone derivative, which is a reactive metabolite. Neither tetracycline nor doxycycline contains the amino acid side chain that has the potential to form a reactive metabolite; this may support the medical experience that neither tetracycline nor doxycycline is associated with HSR [25]. However, certainty regarding the absence of cross-reactivity between minocycline and other tetracyclines is lacking; therefore, caution is advised regarding administration of other tetracyclines in patients who develop a HSR after minocycline.

**Dapsone:** There are several reports of dapsone-induced HSR, also known as the sulfone syndrome [26], with a variety of dermatologic conditions, including leprosy, dermatitis herpetiformis, acne vulgaris, psoriasis, and lupus erythematosus. Dapsone-induced HSR usually occurs 4 or more weeks after initiation of therapy and is typified by fever, rash, and hepatitis [26].

Dapsone is metabolized primarily via two pathways – N-acetylation and N-hydroxylation. N-acetylation is mediated by N-acetyltransferase type 2, whereas N-hydroxylation is mediated primarily by CYP 3A4. Reactive intermediate metabolites produced by N-hydroxylation, such as hydroxylamines, are formed that can induce hemolytic anemia and methemoglobinemia. In addition, these reactive metabolites are involved in the pathogenesis of dapsone-induced HSR [26]. Cimetidine, an inhibitor of CYP 3A4, has been shown to reduce the formation of the toxic hydroxylamine metabolites of dapsone in vitro, but does not affect acetylation of dapsone [27]. Subsequent studies showed that long-term (at least 3 months) concurrent cimetidine results in increased plasma dapsone levels, without an increase in hemolysis, and with reduced methemoglobinemia [28]. Whether or not concurrent use of dapsone and cimetidine also reduces the incidence of dapsone hypersensitivity syndrome is unknown.

**Abacavir:** Abacavir is also associated with a potentially life-threatening adverse reaction in approximately 8% of patients initiated on this drug. HSR from abacavir has been strongly linked to certain human leukocyte antigen (HLA) alleles, especially in white populations [29]. Eighteen Caucasian patients from Western Australia with a history of HHS were compared with 167 control patients. HLA-B*5701 was overrepresented in patients with HHS; it was present in 78% of them and only 2% of controls. The presence of an ancestral haplotype HLA-B*5701, -DR7 and -DQ3 were seen in 72% of patients and none of the control patients – a positive predictive value of 100% and a negative predictive value of 97%. In a North American postabacavir hypersensitivity population, the frequency of HLA-B*5701 was 55%; none of the African American patients in the study possessed the allele [30]. Further studies are needed before genetic testing can be relied upon, as in the decision to rechallenge a patient with abacavir.
Allopurinol: Allopurinol is associated with the development of serious drug reactions, including HSR. In a review of 13 patients with allopurinol adverse reactions, fever, and rash were the most common presenting symptoms. Other associated abnormalities included leukocytosis (62%), eosinophilia (54%), renal impairment (54%), and liver dysfunction (69%) [31]. In a patient who developed a hypersensitivity syndrome reaction with hepatitis, reactivation of HHV-6 occurred. Test for HHV-6 DNA in his blood by PCR analysis was positive. As well, HHV-6 DNA in the cerebrospinal fluid was detected [32]. Allopurinol-induced adverse reactions, including HSR, SJS, and TEN, have been strongly associated with a genetic predisposition in Han Chinese; the HLA-B*5801 allele was found to be an important genetic risk factor [33].

Other medications: Recently, a patient was described who developed an erythematous skin eruption, high fever, generalized lymphadenopathy, and liver and renal dysfunction following both teicoplanin and vancomycin. Infection with HHV-7 and cytomegalovirus had been demonstrated previously. Lymphocyte stimulation tests for teicoplanin and vancomycin were both positive just after recovery and 6 months later [34].

Nevirapine has been associated with HSR involving various combinations of fever, hepatitis or rash. Studies have suggested that HLA-DRB1*0101 and low CD4 counts may increase susceptibility to nevirapine hypersensitivity [35].

Sulphasalazine has also been associated with the development of HSR. In one case, a 33-year-old woman presented with arthralgia, abdominal pain, fever, and an exfoliative dermatitis 4 weeks after starting sulphasalazine for seropositive rheumatoid arthritis [36]. Additional symptoms included facial edema, cervical lymphadenopathy, and tender hepatomegaly. Her liver function tests were severely elevated. The sulphasalazine was discontinued and she was started on prednisone. Despite initial improvement, the patient required a liver transplant but died 3 weeks after surgery from complications.

5.4.3 Differential Diagnosis

The differential diagnosis of HSR includes other cutaneous drug reactions, acute viral infections (e.g., Epstein-Barr virus, hepatitis virus, influenza virus, cytomegalovirus), lymphoma, and idiopathic hypereosinophilic syndrome. Liver transaminases, complete blood count, and urinalysis and serum creatinine should be performed at the initial evaluation. In addition, the clinician should be guided by the presence of symptoms, which may suggest specific internal organ involvement (e.g., respiratory symptoms). Thyroid function tests should be measured and repeated in 2–3 months. A skin biopsy may be helpful if the patient has a blistering or a pustular eruption.

Unfortunately, diagnostic or confirmatory tests to establish drug causation are not readily available. In general, rechallenge, the gold standard to confirm causality, is not justified since the risks outweigh benefits, especially in patients with serious reactions. Similarly, desensitization procedures are not recommended. Skin prick tests have limited value since HSR is not considered to be a specific immune-mediated event. An in vitro testing using a mouse hepatic microsomal system is used for research purposes to evaluate patients who develop HSR [37]. Patch testing has been useful in patients with abacavir HSR [38]. Patch testing has also been helpful in some cases of anticonvulsant-induced HSR [39, 40]. However, the benefit of testing appears to be maximal with certain drugs (i.e., carbamazepine and phenytoin) and for certain clinical manifestations. It should be performed 2–6 months after symptom resolution for best results. The predictive value of patch testing is unknown.

5.4.4 Management

Although the role of systemic corticosteroid therapy is controversial, most clinicians would elect to start prednisone at a dose of 1–2 mg/kg/day if symptoms are severe. Caution is warranted when discontinuing the corticosteroid, as some patients may experience relapse in their condition. A slow tapering over 2–3 months is often necessary. In contrast to the use of corticosteroids in SJS and TEN, there is no significant barrier function alteration (i.e., skin sloughing) leading to the potential for sepsis in the HSR. Cyclosporine [41] or intravenous immunoglobulin (IVIg) [42] has been used in some patients. Antihistamines or topical corticosteroids can also be used to alleviate symptoms. Because the risk of HSR is substantially increased in first-degree relatives of patients who had HSR reactions, counseling of family members is a crucial part of the assessment of this syndrome [10].
HSR is rare but dermatologists are the most likely healthcare provider to make the diagnosis. The causal drug must be stopped immediately and drugs that can cross react must be avoided. Target organs must be identified and corticosteroid use is most helpful when organ failure is possible. Corticosteroid therapy is not always necessary and it can be difficult to withdraw. Symptomatic support is required. Patients and their families should be counseled about relevant drug risks.

References

and hypersensitivity reactions to abacavir. Lancet 359:1121–1122
5.5.1 Etiology and Pathophysiology

Several skin diseases are known to be accompanied by eosinophil infiltration to the dermis or epidermis \([1, 2]\) (Fig. 5.5.1).

Clinical manifestations in these diseases might be induced by eosinophil-derived mediators such as cytokines, chemokines, lipid mediators, superoxide, or cytotoxic granular proteins as summarized \([3–5]\) in Fig. 5.5.2. Eosinophils are major skin infiltrating cells in Th2 cytokine-mediated allergic cutaneous inflammation in which Th2 cytokines, such as interleukin (IL)-4, IL-5, and IL-13 are produced by Th2-type helper T cells or resident mast cells \([6, 7]\).

Eosinophils are activated by various inflammatory mediators through surface or cytoplasmic receptors (Table 5.5.1). Circulating eosinophils migrate to inflammatory sites from blood vessels through the interaction of E/P selectins \([8]\) with their ligands or adhesion molecules such as VCAM-1 with VLA4 \([9]\). Eosinophil then migrates in response to chemokines such as eotaxin (CCL3) through its receptor CCR3. Eotaxin is generated by fibroblasts by Th2 cytokines such as IL-4, IL-13, and/or tumor necrosis factor (TNF-\(\alpha\)).

At present, tissue eosinophilia seems to be a characteristic feature of Th2-polarized disease, but weak or moderate eosinophil infiltration is observed even in Th1-polarized disease \([10–12]\). In this context, the involvement of eosinophil chemoattractants other than eotaxins has been postulated. Recent studies have revealed that interferon (IFN-\(\gamma\), a Th1 cytokine) stimulates human fetal fibroblast-1 cells to produce the potent eosinophil chemoattractant galectin-9 \([13]\) or RANTES. Therefore, eosinophils participate in Th2- or Th1-mediated skin disease via different chemotactic stimulations.

5.5.2 Clinical Characteristics and Diagnosis

Several skin diseases are known to be accompanied by eosinophil infiltration to the dermis or epidermis. Usually, these diseases are induced by Th2-mediated allergic mechanisms with erythematous cutaneous response and, pruritic sensation.
5.5.2.1 Atopic Dermatitis

Atopic dermatitis (AD) is the most common Th2-mediated allergic disease with atopic background in the family. Characteristic distribution of eczematous skin lesions with elevated serum IgE, increased eosinophil count, and intolerable pruritic sensation are important clues for diagnosis. Degranulated eosinophils are prominent features of acute phase of eczematous reaction or patch test-site with mite antigens [14].

Eotaxin, eosinophilactic chemokine is strongly expressed by the resident fibroblasts in the patient with AD (Fig. 5.5.3).
5.5 Eosinophilic Dermatoses

**Table 5.5.1** Receptors expressed by eosinophils

<table>
<thead>
<tr>
<th>Receptor Type</th>
<th>Receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fe Receptor</td>
<td>Fc γR, Fc αR, Fc εR</td>
</tr>
<tr>
<td>Complement receptor</td>
<td>C3a, C5a</td>
</tr>
<tr>
<td>Integrin</td>
<td>Mac-1, LFA-1, VLA-4</td>
</tr>
<tr>
<td>Cytokine receptor</td>
<td>IL3, IL5, GMCSF</td>
</tr>
<tr>
<td>Chemokine receptor</td>
<td>CCR1, CCR3</td>
</tr>
<tr>
<td>Eicosanoid receptor</td>
<td>CysLT1, B-LTR, CRTH2</td>
</tr>
<tr>
<td>Histamine receptor</td>
<td>H1, H2, H4</td>
</tr>
<tr>
<td>Others</td>
<td>PAFR, FAS, LA-DR, fMLP</td>
</tr>
</tbody>
</table>

Enhanced production of eotaxin by dermal fibroblasts derived from AD is thought to be responsible for massive eosinophil infiltration in the dermis of AD (Fig. 5.5.4).

### 5.5.2.2 Prurigo

Prurigo is a relatively common pruritic papular skin disease mainly divided into the acute, subacute, and chronic forms. The cause and associated conditions are unknown in many cases except for insect-bite reactions. However, it is occasionally observed in the patients with AD, or human immunodeficiency syndrome in addition to hematological disorder, liver dysfunction or renal diseases with tissue eosinophilia and peripheral nerve elongation [15]. Prurigo may resolve after treatment of the underlying condition, but it is often difficult to control intolerable itch sensation.

Accordingly, in chronic cases that often do not respond to steroid treatment, persistent pruritus significantly affects the patients’ quality of life.

### 5.5.2.3 Bullous Pemphigoid

Bullous pemphigoid is an autoimmune bullous disease characterized by subepidermal blister with massive eosinophil infiltration. Depositions of Immunoglobulin G and complement along basement membrane zone are important clues to make a correct diagnosis [16]. Presently, detection of BP180 (type 17 collagen) by western blot analysis or ELISA are available at commercial level. Recently we reported that clinical and pathological features very similar to bullous pemphigoid including eosinophil infiltration and mast cell activation are observed in generalized atrophic benign epidermolysis bullosa (GABEB), a subtype of junctional epidermolysis...
bullosa (JEB), an autosomal recessive disorder [17]. These clinical manifestations showed good response to oral corticosteroid [18].

### 5.5.2.4 Ofuji Disease (Eosinophilic Pustular Folliculitis)

This rare but distinct skin disease was first reported by Ofuji et al in 1970 [19]. First, it was reported to have preferentially occurred in oriental population, but in a recent year, occidental cases have been reported from western country especially in the patients with human immuno deficiency syndrome. Characteristic features of Ofuji disease is well-defined annular lesions surrounded by follicular pustules mimicking superficial fungal disease. Eosinophils predominantly infiltrate around hair follicles with spongiotic change (Fig. 5.5.5).

### 5.5.2.5 Hypereosinophilic Syndrome

Hypereosinophilic syndromes are a group of poorly treated diverse disorders characterized by sustained peripheral blood and/or tissue eosinophilia. In some cases, these are accompanied by severe pulmonary or cardiovascular involvements [20]. Episodic angioedema with eosinophilia (Gleich disease) is now thought to be a severe form of hypereosinophilic syndrome [21].

### 5.5.3 General Therapeutic Outline (Table 5.5.2)

#### 5.5.3.1 Glucocorticoid

Glucocorticoid is the most widely prescribed drug to treat allergic inflammatory skin diseases in the world.

![Eosinophilic pusutular folliculitis](image)

**Fig. 5.5.5** Clinical (left) and histopathological features (right) of Ofuji disease
<table>
<thead>
<tr>
<th>Drugs</th>
<th>Target molecules, receptors</th>
<th>Effect on eosinophils</th>
<th>Reported cases</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical steroid</td>
<td>GRα, IκB, GRE</td>
<td>Induction of apoptosis of eosinophils</td>
<td>ACD, AD etc</td>
<td>[22–24]</td>
</tr>
<tr>
<td>Calcineurin inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Immunophilin (macrophilin 12)</td>
<td>Inhibitions of CCR3, RANTES expressions</td>
<td>AD</td>
<td>[26]</td>
</tr>
<tr>
<td>Pimecrolimus</td>
<td>Immunophilin (macrophilin 12)</td>
<td>Suppression of eosinophil migration</td>
<td>AD</td>
<td>[35]</td>
</tr>
<tr>
<td>Immunomodulator</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D3</td>
<td>D3R</td>
<td>Suppression of eotaxin production</td>
<td>Prurigo</td>
<td>[31]</td>
</tr>
<tr>
<td>Anti-allergic agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihistamine</td>
<td>H1R, H2R, H4R</td>
<td>Suppression of eosinophil migration</td>
<td>AD, UR, ACD</td>
<td>[25]</td>
</tr>
<tr>
<td>Leukotriene inhibitor</td>
<td>B-LTR, CysLT1</td>
<td>Suppression of eosinophilia</td>
<td>UR</td>
<td>[40]</td>
</tr>
<tr>
<td>Thromboxane A2 inhibitor</td>
<td>CRTH2</td>
<td>Suppression of eosinophil migration</td>
<td>Kimura disease, Ofuji diseasea</td>
<td>[3, 29]</td>
</tr>
<tr>
<td>Th2 cytokine inhibitor</td>
<td>IL4R (Th2), IL5R (eosinophil)</td>
<td>Suppression of eosinophilia</td>
<td>AD</td>
<td>[27, 28]</td>
</tr>
<tr>
<td>Mast cell stabilizer</td>
<td>NK1R?</td>
<td></td>
<td>AD</td>
<td></td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic glucocorticoids</td>
<td>GRα, IκB, GRE</td>
<td>Inhibition of eotaxin, IL5 production</td>
<td>ACD, AD, UR etc</td>
<td>[22–24]</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Immunophilin</td>
<td>Inhibition of eotaxin, IL5 production</td>
<td>AD, Ofuji’s PEa Kimura diseasea</td>
<td>[35, 41]</td>
</tr>
<tr>
<td>CpGDNA</td>
<td>TLR9</td>
<td></td>
<td></td>
<td>[34]</td>
</tr>
<tr>
<td>Anti-IL5 antibody</td>
<td>IL5R</td>
<td>Suppression of eosinophilia</td>
<td>Allergic Asthma, ADa</td>
<td>[32]</td>
</tr>
<tr>
<td>NFXB Decoy</td>
<td>NFXB</td>
<td>Suppression of eosinophil infiltration to the skin</td>
<td>ADb</td>
<td>[35]</td>
</tr>
<tr>
<td>STAT6 Decpy</td>
<td>STAT6</td>
<td>Suppression of eosinophil infiltration to the skin</td>
<td>ADc</td>
<td>[33]</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>IFN-γR, STAT1, JAK1</td>
<td></td>
<td>Prurigo, AD, Ofuji disease</td>
<td>[37, 42, 43]</td>
</tr>
</tbody>
</table>

ACD allergic contact dermatitis; AD atopic dermatitis; PE papuloerythroderma; UR urticaria
a Personal communications
b Phase 3 clinical trial
c Open trial
Oral, topical, and inhaled glucocorticoids are used in daily practice. It is well-known that glucocorticoids suppress inflammatory response to downregulate transcriptional factors such as NFKB or AP-1; both of these factors activate various kinds of cytokine or chemokine genes involved in eosinophil activation or chemokinesis \[22, 23\]. In addition to the above genomic actions, glucocorticoid possesses potent apoptosis inducing activity on eosinophils or lymphocytes \[24\]. Therefore, glucocorticoid is the first line-drug to treat skin disease with eosinophil infiltration.

### 5.5.3.2 Antihistamine

Histamine is the first mediator to be associated with allergic reactions and was the first whose inhibition proved useful in the management of allergic diseases \[25\]. Recently many antihistaminic drugs have been available with less side effects such as sedation and dry mouth. These new drugs not only inhibit histamine-induced vascular reactions or pruritic sensation but also downregulate eosinophil activating-cytokine or chemokine production from lymphocytes or skin resident cells.

### 5.5.3.3 Immuno Suppressants

Topical or oral immuno suppressants are used for severe AD, prurigo or other dermatoses with eosinophil infiltrations \[26\]. These include tacrolimus, pimecrolimus or cyclosporine. Cyclophosphamide, methotrexate or azathioprine are occasionally used to control severe systemic vasculitis such as Churg-Strauss syndrome or polyarteritis nodosa or hypereosinophilic syndrome.

### 5.5.4 Current Established Therapy

#### 5.5.4.1 Th2 Cytokine Modulator

Supltast tosilate (IPD\textsuperscript{®}), the selective Th2 cytokine suppressor, has been reported to inhibit IL4 or IL5 production from Th2 cells, to suppress eosinophil migration or to downregulate cell adhesion molecule expressions by vascular endothelial cells \[27\]. It has been mainly prescribed in Japan and reported to be effective for severe asthma, allergic pollenosis or refractory AD. Recently we studied to evaluate the clinical effects on severe adult-type AD. We obtained the clinical data that IPD showed significant improvement of skin symptoms compared with the control group especially in the patients with high value of immunoglobulin E and basophils (manuscript is submitted) \[28\].

#### 5.5.4.2 Thromboxane A2 (TXA2) Inhibitors

There is some evidence from basic research and clinical reports to indicate that TxA2 is involved in the onset and development of certain allergic diseases with eosinophil infiltration. There are two types of TxA2 inhibitors in clinical use in Japan, including TxA2 synthetase inhibitor (ozagrel) and TxA2 receptor antagonists (ramatroban and seratrodust). Although all these TxA2 inhibitors are applied for the treatment of bronchial asthma, there are some reports that these drugs improved refractory urticaria, Kimura’s disease (personal communication) or Ofuji disease. Several investigators revealed the efficacy and antagonistic action of ramatroban against CRTH2, one of the prostaglandin D2 receptors using rodent models \[29, 30\]. However, further studies are necessary to fully determine the efficacy of these anti-CRTH2 agents.

#### 5.5.4.3 Topical Vitamin D3

Th2-mediated allergic diseases including AD, contact dermatitis, or prurigo are relatively common skin diseases; all of these are characterized by intolerable itch sensation resulting in marked scratching and papular eruption formation. Topical steroid ointment or intralesional steroid is the first choice of dermatological therapy. Recently we have reported that topical vitamin D3 ointment significantly improved steroid resistant prurigo \[31\].

We conducted topical vitamin D3 therapy to 32 patients refractory to various treatments including
steroids. Vitamin D₃ ointment was applied once or twice daily, and assessments were performed at weeks 4 and 8 after starting treatment. Twenty-four of the 32 patients showed improvement or much improvement, which was especially significant in the chronic cases. In a preliminary study, we found that vitamin D₃ down regulates IL4 induced eotaxin production from prurigo derived fibroblasts (Fig. 5.5.6 right, manuscript in preparation). Figure 5.5.6 (left) shows the clinical response of topical vitamin D₃ ointment to refractory prurigo in HIV patient.

5.5.5 Experimental Approaches

5.5.5.1 Anti IL5 Antibody

IL-5 is a Th2 cytokine involved in regulating several aspects of eosinophil survival including their production, activation, and tissue recruitment and antiapoptotic effect.

First clinical trial of anti-IL5 antibody therapy was conducted in the patients with allergic asthma and gave unfavorable clinical results [32]. However, anti-IL5 antibody therapy has been reevaluated for the treatment of refractory AD.

5.5.5.2 STAT6 Decoy

Signal transducers and activators of transcription 6 (STAT6) play a crucial role in the transactivation of IL-4 and IL-13 which might be involved in the pathogenesis of AD. We reported that the IgE-mediated late phase reaction significantly decreased in STAT6 deficient (STAT6/-) mice than in AD model mice. We therefore hypothesized that synthetic double-stranded DNA with a high affinity for STAT6 could be introduced in vivo as decoy cis elements to bind the transcriptional factor and to block the gene activation contributing to the onset and progression of AD, thus providing effective therapy for AD. Treatment by the transfection of STAT6 decoy oligodeoxynucleotides (ODN), but not scramble decoy ODN after the sensitization by anti-DNP-IgE antibody, had a significant inhibitory effect on not only STAT6 binding to nuclei but also late phase response. A histological analysis revealed that both edema and the infiltration of neutrophils and eosinophils significantly decreased in STAT6 decoy ODN transfected mice. At present, STAT6 decoy ointment is under clinical investigation for the treatment of refractory AD and we obtained promising effect [33]. Other promising therapies including CpG-oligodeoxynucleotides, NFκB decoy or biologics are under clinical trials [34, 35].
5.5.6 Complications to Avoid

As well-known, most of the drugs used to control tissue eosinophilia possess immunosuppressing activity; therefore, cutaneous or systemic microbial infections should be carefully monitored in addition to undesirable side effects on the skin after long-term topical steroid.

5.5.7 Global Variations

It is now universally accepted that immunosuppressants including glucocorticoid, or calcineurin inhibitors, both in topical and systemic use, are the first choice to control allergic inflammation with eosinophil infiltrations, especially for the management of AD/eczema. Oral antihistamine or other anti-allergic drugs have been reported to modulate eosinophil function in addition to their known pharmacological actions.

There are some global variations for the treatment of certain eosinophilic dermatoses. Among these, eosinophilic pustular folliculitis first described by Ofuji et al. [36] shows some therapeutic variations in the world. In Asian counties including Japan, oral indomethacin has been reported to show a good response within 2–4 weeks [37, 38]. In Europe, this disease is frequently associated with HIV or occurs in children. IFN-α 2b or other drugs such as dapsone or isotretinoin are preferentially used although their exact mechanisms for eosinophil functions remain unanswered [37, 39].

In conclusion, some drugs are available only in Japanese market or some diseases show racial differences; therefore, closer relationship among dermatologists is required to share clinical, pharmacological, and basic information in the state of global variations.

Take Home Message

> Eosinophilic dermatoses are frequently accompanied by intolerable pruritic sensation resulting in impaired patients’ QOL. Therefore, antipruritic therapy in combination with anti-allergic therapy is required to control these refractory diseases.

References


5.6.1 Pyoderma Gangrenosum

5.6.1.1 Etiology and Pathophysiology

The pathogenesis of PG is unknown. Multiple abnormalities of humoral immunity, cell-mediated immunity, and neutrophil function have been reported, although the pathogenetic significance of these findings remains an enigma. The role, if any, of a vasculitis in the pathogenesis of PG is debatable.

5.6.1.2 Clinical Characteristics and Diagnosis

There are several variants, including classic, peristomal, pustular, bullous, and vegetative types [1], which have different characteristics as described below. The most common one is classic PG.

It has been demonstrated that the type and severity of associated systemic diseases influence the prognosis of PG. It seems likely that successful treatment of the associated diseases results in the improvement or even the complete remission of PG. In contrast, their unresponsiveness to the treatment results in poor prognosis.

Although the histological findings are nonspecific and heterogeneous among its variants, histopathologic examination can help differentiate from PG-mimicking skin diseases, i.e., Wegener’s granulomatosis, polyarteritis nodosa, antiphospholipid syndrome, lymphoma, and sporotrichosis. Pathergy occurs in 25–50% of cases, in which the lesions develop at the site of minor trauma and so surgery or debridement is generally contraindicated.

Tendency to progress is high in most patients and so an urgent referral to the dermatology department is required. Early diagnosis and prompt treatment reduce the risk of scars and disfigurement.

5.6.1.2.1 Classic PG

Classic PG can occur on any skin surface but is commonly seen on the frontal surface of the legs. This presents as a deep ulcer with a violet or blue, well-defined border (Fig. 5.6.1). The edge of the ulcer is often undermined, and the surrounding skin is erythematous and indurated. The ulcer often starts as a small papulo-nodule, subsequently forming small ulcers. These ulcers often coalesce and undergo necrosis at the central area. The lesions are usually painful, and the pain can be insupportable. When the lesions regress spontaneously or in response to the successful
treatment, they leave cribriform scars. Patients often have systemic symptoms such as fever, malaise, arthralgia, and myalgia.

### 5.6.1.2.2 Peristomal PG

Peristomal PG, which has a similar morphology as classic PG, occurs near abdominal stomas. Characteristically, most patients have inflammatory bowel disease (IBD), although this may occur in the patients with the stomas who went through an ileostomy or colostomy for other intestinal diseases.

### 5.6.1.2.3 Pustular PG

Pustular PG is a rare superficial variant of the disease. The lesion often begins as a painful pustule or a crop of pustules on the trunk and extensor surfaces of the limbs that later coalesce into ulcer(s). Pustular PG is also seen in patients with IBD [2].

### 5.6.1.2.4 Bullous PG

Bullous PG is also a superficial variant with predilection sites of the upper limbs and face. This form of the disease presents as concentric bullous areas that spread rapidly. They may form more superficial ulcers with the undermined edges than those in classic type. It is associated mostly with hematological conditions, and the prognosis is often poor when the patients have the underlying hematological malignancy [3].

### 5.6.1.2.5 Vegetative PG

Vegetative PG is a superficial and less aggressive form of the disease than other variants. It usually occurs as a single lesion and may respond well to local treatment even without systemic one.

### 5.6.1.3 General Therapeutic Outline

Since few controlled trials of treatment have been done so far, the treatment is largely empirical and often depends on local experience. Most clinicians use both topical and systemic treatments. Immunosuppression is the mainstay of treatment, and the most commonly used drugs are corticosteroids and cyclosporine. Several other immunosuppressive agents, drugs or treatment targeting neutrophils, plasmapheresis have been used with varied results.

### 5.6.1.4 Current Established Therapies

According to the recent review of the literature, therapeutic efficacy of systemic treatment with corticosteroids and cyclosporine is best documented in the literature [4]. In another review [1], they recommended oral corticosteroids with or without minocycline as first line treatment. In cases that do not respond to these treatments, the first group recommended alternative therapeutic procedures, above mentioned systemic treatment in conjunction with mycophenolate mofetil, tacrolimus, infliximab, or plasmapheresis. The second group recommended infliximab as this has fewer recognized side effects than cyclosporine.

#### 5.6.1.4.1 Topical Treatments

Highly potent topical corticosteroids or topical tacrolimus may be sufficient to induce remission especially for patients with localized or superficial PG [5, 6]. Injection of triamcinolone 40 mg/mL into the ulcer edge may be effective either alone or as an adjunct to systemic treatment. Most investigators have stressed the importance of early topical treatment because it is more likely to succeed when the ulcer is small. Topical
therapy can be considered as first-line therapy in cases of localized PG or that of classic PG where systemic immunosuppressive therapy should be avoided for infectious diseases.

### 5.6.1.4.2 Systemic Corticosteroids

Most patients need systemic treatment to induce remission. Prednisolone is the drug of choice and is usually started at high doses (60–120 mg) [7]. Minocycline 100 mg twice daily may be of some benefit to reduce the amount of oral steroids [8]. Rapid improvement has been reported in patients with severe disease by pulse therapy with intravenous methylprednisolone of 1 g daily for 3–5 days [7].

### 5.6.1.4.3 Cyclosporine

When PG does not respond to corticosteroid therapies, cyclosporine is the most widely used alternative [4]. Most patients show a clinical improvement within 3 weeks with a dose of 3–5 mg/kg/day [9]. Cyclosporine has several serious side effects, including nephrotoxicity, hypertension, and increased risk of cancer.

### 5.6.1.4.4 Other Immunosuppressants

Azathioprine, used alone or in combination with corticosteroids, has had variable results [7].

### 5.6.1.4.5 Antitumor Necrosis Factor Agents

PG has been reported to respond to biologic therapeu tic agents against tumor necrosis factor-alpha including infliximab [10] and etanercept [11]. In a randomized controlled trial, infliximab (5 mg/kg) has been reported to be superior to placebo [12].

### 5.6.1.5 Experimental Approaches

In some case reports of PG patients without associated disease, intravenous immunoglobulin (IVIg) [13], granulocyte and monocyte absorption apheresis (GCAP) [14], as well as plasmapheresis [15] and cyclophosphamide treatment appeared to be effective. These therapies should be applied in patients who do not respond to standard treatments.

Systemic antibiotics, including tetracyclines, vancomycins, rifampicin, and mezlocillin, may also modulate the course of PG through anti-inflammatory mechanisms in addition to their role in inhibiting secondary bacterial infections.

### 5.6.1.6 Complications to Avoid

Systemic immunosuppressants are the mainstay of treatment for PG. However, prolonged therapy is associated with significant side effects. Long-term systemic glucocorticosteroid therapy may result in iatrogenic Cushing’s syndrome and may predispose the patient to infection of the wounds.

Long-term side effects of cyclosporine include nephrotoxicity, hypertension, and an increased risk of malignancy. Other treatments, including azathioprine, alkylating agents, infliximab, or tacrolimus have also been shown to be associated with long-term side effects; especially local or systemic infection, particularly in elderly patients with PG or in those patients in a reduced state of health.

### Take Home Messages

- A biopsy should be avoided except the time when you need to exclude other skin diseases.
- The treatment is largely empirical.
- Therapeutic efficacy of systemic treatment with corticosteroids and cyclosporine is best documented in the literature and should be considered first-line therapy.
- Infliximab has been proven to be more effective than placebo in a small randomized controlled trial.

### 5.6.1.7 Global Variation

No variation.
5.6.2 Sweet’s Syndrome

Key Features

› Sweet’s syndrome (SS) is associated with malignancy or medication
› Variability of the composition and location of the cutaneous inflammatory infiltrate suggest related extra-cutaneous conditions.

5.6.2.1 Etiology and Pathophysiology

The etiology and pathophysiology of SS remains to be elusive, although cytokines may play an important etiologic role in the pathogenesis of this dermatosis [16].

As for SS associated with leukemia cutis, there have been several suggestions. First, the leukemic cells within the skin lesion represent a specific infiltrate. Second, the circulating immature myeloid cells are recruited to the skin as innocent bystanders during inflammatory responses. Finally, the atypical cells of leukemia cutis develop into mature neutrophils as a result of their granulocyte colony stimulating factor (G-CSF)-induced differentiation [17].

5.6.2.2 Clinical Characteristics and Diagnosis

The main features of SS are fever, elevated neutrophil count, painful red papulo-nodules, and plaques [18]. There are at least three types of cutaneous lesion, i.e., (1) classical nonpustular, (2) superficial pustular and (3) subcutaneous types as described later. Women between the age of 30 and 50 years are predisposed to classical SS. The fever can precede the skin disease or both are present together. Other symptoms include arthralgia, general malaise, headache, and myalgia. Several conditions have been observed related to SS [19]. Probably related conditions include cancer, infections, IBD (Crohn’s disease and ulcerative colitis), and pregnancy, while possibly-related diseases are Behçet’s disease, erythema nodosum, rheumatoid arthritis, sarcoidosis, and thyroid diseases. SS occurring in a patient with a hematologic disorder, may present as a paraneoplastic syndrome, a drug-induced dermatosis, or coincident with leukemia cutis [17]. The hematologic disorder includes acute myelocytic leukemia, myelodysplastic syndrome, and chronic myelocytic leukemia. In most cases of drug-induced variants, G-CSF is responsible for the induction of the lesions.

Extracutaneous manifestations of SS can affect the mucosa of the mouth and eye, the bone, central nervous system, kidney, intestine, liver, heart, bronchus, lung, muscle, and spleen. Ulcers of the oral mucosa are often found in patients with hematologic disorders. The oral lesions resolve after the initiation of treatment with systemic corticosteroids.

Histologically, there is an infiltrate of mature neutrophils in the superficial dermis. The distribution is typically dense and diffuse, although less commonly it has been noted to be perivascular. In occasional cases, lymphocytes or histiocytes may be predominantly present in the inflammatory infiltrate. In addition, eosinophils have been noted in the cutaneous lesions of some patients with either classical or drug-induced SS. Swelling of the endothelial cells, dilatation of the small blood vessels, and leukocytoclasia are also frequently present. Usually, neither fibrin deposition nor neutrophils are present within the vessel wall.

5.6.2.2.1 Classical, Nonpustular Lesions

The skin lesions of SS typically appear as tender, red or purple–red, papules or nodules on the face, neck, and the upper extremities (Fig. 5.6.2). The lesions enlarge over a period of days to weeks. The individual lesions may coalesce to form irregular, sharply demarcated plaques. The lesions may have a vesicle- or bulla-like eruption due to the pronounced edema in the upper dermis. They usually resolve spontaneously or after treatment without scarring. Skin lesions recur in one-third to two-thirds of the patients. The lesions can occur at the sites of biopsies or other trauma.

5.6.2.2.2 Superficial or Pustular Lesions

Less commonly, SS can present as a pustular dermatosis. This clinical variant includes patients with pustular eruption of ulcerative colitis (UC) [20] and those with neutrophilic dermatosis of the dorsal hands proposed by Galaria et al. [21].
5.6.2.4 Current Established Therapies

The therapeutic mainstay for SS is systemic corticosteroids [23]. Drugs targeting neutrophils such as colchicine and potassium iodide has been used a first-line therapy in patients with either classical or malignancy-associated SS.

5.6.2.4.1 Systemic Corticosteroids

Oral prednisone therapy often starts at doses of 30–60 mg, tapering to 10 mg within 4–6 weeks. In some patients showing recurrences, daily or alternate-day treatment is needed at lower prednisone doses of 10–30 mg for 2 or 3 months. The patients with refractory disease may be successfully managed by daily pulse intravenous administration of 1 g of methylprednisolone for 3–5 consecutive days [24].

5.6.2.4.2 Topical Corticosteroids

Localized SS lesions may be treated topically with high-potency corticosteroids, such as 0.05% clobetasol propionate [25]. Alternatively, intralesional corticosteroids can be used.

5.6.2.4.3 Potassium Iodide and Colchicine

The improvement of SS lesions with oral potassium iodide at a dose of 900 mg/day was described by different groups [26, 27]. Successful management of SS using colchicine has also been confirmed in larger studies [28].

5.6.2.5 Experimental Approaches

The successful management of SS with indomethacin was reported [29]. However, as the efficacy of indomethacin is controversial, this therapy should be applied in patients who are not severe and do not respond to standard treatments.

Monotherapy with cyclosporine has also been used to treat SS patients [30], more frequently as a corticosteroid-sparing agent or a second-line drug when first-line therapies have failed. Similarly, dapsone has been used either as monotherapy or in combination therapy for the treatment of patients with SS.

5.6.2.3 General Therapeutic Outline

In patients with the classical form of SS, it may eventually resolve without therapeutic intervention. The initiation of systemic corticosteroid therapy usually results in prompt improvement, even malignancy-associated one. Improvement and clearing of the lesions may occur following successful treatment of a dermatosis-related cancer or discontinuation of a causative medication in patients with malignancy-associated SS or drug-induced SS, respectively. Surgical treatment has also resulted in the resolution of SS in patients with tonsillitis or solid tumors.

5.6.2.2.3 Subcutaneous Lesions

The lesions may mimic erythema nodosum when they are located on the legs [22]. Pattern of inflammatory infiltrates within the subcutaneous fat can be lobular, septal, or combined.

Fig. 5.6.2 Sweet’s syndrome
Systemic therapy directed toward *Staphylococcus aureus* may partially improve or resolve SS skin lesions after treatment with antimicrobials, such as doxycycline, minocycline, tetracycline, or other systemic antimicrobials.

The effective treatment of SS with other agents has also been reported in uncontrolled studies or single case reports. Successful treatment of SS with clofazimine has been reported in two groups. These include intralesional and systemic interferon-alpha, and etretinate [31].

### 5.6.2.6 Complications to Avoid

Malignancy and IBDs.

### 5.6.2.7 Global Variation

As oral retinoids, etretinate has been replaced by acitretin in the US and Europe, but etretinate is available only in Japan.

### Take Home Message

› SS is often cancer-related
› Responds well to systemic corticosteroid or drugs targeting neutrophils such as colchicine and potassium iodide

### 5.6.3 Erythema Elevatum Diutinum

#### Key Features

› Acute lesions of red or purple papules of erythema elevatum diutinum (EED) are predominantly located on the extensor parts of the arms and legs.
› Chronic lesions are fibrous tumors, which may resemble xanthomas.
› The histology is polymorphous.

#### 5.6.3.1 Etiology and Pathophysiology

Etiology of EED is unknown, although it is thought to be a variant of leukocytoclastic vasculitis resulting from an Arthus-type reaction to bacterial or viral antigens. Immune-complexes may play a role in EED. It has also been reported that interleukin (IL)-8 is responsible for a selective recruitment of leukocytes to the lesional skin. In some cases, infections may induce EED.

#### 5.6.3.2 Clinical Characteristics and Diagnosis

EED is a rare dermatosis presenting as persistent red, violaceous and yellowish papules, plaques, and nodules. Most often, EED presents as multiple symmetrical lesions over the extensor aspects of the extremities and are usually located near joints such as the fingers, hands, elbows, ankles and knees [32]. In some cases, nodules are surrounded by vesicles and bullae. Onset is usually in middle life. Lesions may involute after 5–10 years, while it may persist for more than 20 years.

The histological appearance varies according to the age of the lesions. In early phase, there is a moderately dense perivascular infiltrate of neutrophils within and around the walls of small dermal blood vessels. These may show swelling of the vascular endothelial cells and leukocytoclasia. There are small numbers of histiocytes and lymphocytes. In established lesions, the infiltrate of neutrophils involves the entire dermis. In the epidermis, focal spongiosis or epidermal necrosis might be present. The number of capillaries increases in this phase.

In late phase, there is variable fibrosis and in some cases a proliferation of spindle-shaped fibroblasts. Small foci of neutrophilic vasculitis are sometimes found even in the fibrotic areas.

Although the clinical features are relatively distinct, the histological findings of early lesions may be indistinguishable from other neutrophilic dermatoses. EED differs from granuloma faciale in the predominance of neutrophils rather than eosinophils.

As SS and PG, arthralgia and pulmonary infiltrates may occur. An association with myelodysplastic syndrome, lymphoma, multiple myeloma, IgA monoclonal gammopathy, and cryoglobulinema has been
documented. Patients with EED may have infections, IBD, and plasma-cell dyscrasia [33].

### 5.6.3.3 General Therapeutic Outline

Dapsone or sulphonamides are first-line treatment for EED. If any, treatment of the underlying cause should be targeted.

### 5.6.3.4 Current Established Therapies

Most patients respond to dapsone. It is used between 50 and 100 mg daily.

### 5.6.3.5 Experimental Approaches

Other therapies employed include niacinamide, tetracycline, colchicine, intralesional, topical or oral corticosteroids, and chloroquine.

### 5.6.3.6 Complications to Avoid

Hematological diseases and IBDs.

### Take Home Messages

- The typical clinical presentation of EED is erythematous papules and plaques involving the extensor surfaces of the extremities.
- Histologically, there is a spectrum from leukocytoclastic vasculitis to vessel occlusion and dermal fibrosis.
- Establishing the diagnosis of EED is important so that appropriate screening for associated conditions can ensue.

### 5.6.3.7 Global Variation

There is no variation.

### 5.6.4 Subcorneal Pustular Dermatosis (Sneddon-Wilkinson’s Disease)

#### Key features

- Asymptomatic pustules, grouped in an annular pattern, are located around the axillary and inguinal folds mainly in middle-aged women.
- Subcorneal pustular dermatosis (SPD) is defined by unilocular, subcorneal pustules.

#### 5.6.4.1 Etiology and Pathophysiology

The etiology and pathogenesis remain unknown. Increased tumor necrosis factor-alpha in the sera of patients with SPD, may be responsible for the activation of neutrophils.

#### 5.6.4.2 Clinical Characteristics and Diagnosis

SPD is a chronic, relapsing, vesiculopustular disease. Predilection sites are the trunk, particularly intertriginous areas, and flexor aspect of limbs. They are sterile, but secondary infection sometimes develops. It usually spares the mucous membrane. The condition is more common in women in their fourth and fifth decades of life. The pustules are flaccid that are surrounded by a transient erythematous flare in the early stages.

The subcorneal pustule is filled with neutrophils and an occasional eosinophil. Neutrophils can be found in the epidermis, although they do not form spongiform pustules basically.

IgA pemphigus should be ruled out. In this condition, IgA intercellular deposits are directed against interkeratinocyte adhesion molecule. Circulating IgA antibodies are present in approximately half of the cases.

SPD-like drug-induced pustular eruptions have been reported following ingestion of isoniazid, diltiazem, paclitaxel, cephalosporins, amoxicilime, dapsone, and quinidine sulfate.
5.6.4.3 General Therapeutic Outline

Dapsone is the first choice of the treatment. Dapsone-responsiveness has been used as a diagnostic criterion [34].

5.6.4.4 Current Established Therapies

Most patients respond well to dapsone. It is used between 50 and 200 mg daily. Once control has been established, the dose can be tapered to the minimum required level. Sulfapyridine and sulfamethoxypyridazine have also been used as alternatives, but are generally less effective.

Oral corticosteroids are regarded as being less effective, but they have been used successfully. Oral corticosteroids have been more commonly used in combination with dapsone, usually to help treat an associated condition such as PG, multiple myeloma, or systemic lupus erythematosus. Topical potent corticosteroids have also been successfully used alone and as an adjunct to dapsone.

5.6.4.5 Experimental Approaches

Etretinate has been used as an alternative treatment with doses range between 20 and 75 mg daily, presumably equating to 0.25–1 mg/kg/day. It has also been combined with dapsone to maintain control. More recently, acitretin has been used. Isotretinoin has been shown not to control SPD.

Narrowband (TL-01) UVB, broadband UVB, PUVA, and re-PUVA, have all been reported as being successful in controlling SPD.

In resistant or intolerant cases, cyclosporine has been used in combination with systemic steroid, dapsone, or acitretin [35].

5.6.4.6 Complications to Avoid

Cutaneous secondary infection and IgA gammopathy. A small number of patients have had an associated gammopathy, most commonly of IgA type.

5.6.4.7 Global Variation

As oral retinoids, etretinate has been replaced by acitretin in the US and Europe, but etretinate is available only in Japan.

5.6.5 Rheumatoid Neutrophilic Dermatosis

5.6.5.1 Etiology and Pathophysiology

Rheumatoid neutrophilic dermatosis (RND) occurs in patients with severe, seropositive rheumatoid arthritis. Clinical symptoms are erythematous plaques and periarticular nodules.

5.6.5.2 Clinical Characteristics and Diagnosis

The etiology of RND is largely unknown. The release of cytokines such as IL-6 and IL-8 may be associated with the development of RND.

RND is a rare cutaneous manifestation of severe rheumatoid arthritis. It presents with plaques and nodules overlying joints and the extremities, particularly the hands [36]. The lesions may be asymptomatic, but are frequently mildly tender. There is a case of RND in a
patient with seronegative, rheumatoid arthritis [37] and palindromic-type rheumatism.

Histologically, there is a dense neutrophilic infiltrate throughout the dermis, but particularly in the upper and middle ones. There may be leukocytoclasia, but no vasculitis. In older lesions, lymphocytes, plasma cells and macrophages containing neutrophilic debris are also present.

5.6.5.3 General Therapeutic Outline

Hydroxychloroquine, dapsone, cyclophosphamide and topical steroids.

5.6.5.4 Current Established Therapies

The treatment of the choice includes hydroxychloroquine, dapsone, cyclophosphamide and topical steroids. Resolution of the lesions occurs spontaneously or with the improvement of the course of RA, but lesions tend to recur with exacerbation of the RA, as observed in our case.

5.6.5.5 Experimental Approaches

Systemic corticosteroid treatment might be efficacious.

5.6.5.6 Complications to Avoid

Seropositive and seronegative rheumatoid arthritis.

5.6.5.7 Global Variation

No variation.

5.6.6 Neutrophilic Eccrine Hidradenitis (NEH)

Key Features

- NEH is a rare complication of induction chemotherapy used in the treatment of cancers.
- The combination of neutrophilic infiltration and necrosis of the eccrine secretory gland epithelium is highly characteristic for NEH.

5.6.6.1 Etiology and Pathophysiology

Etiology and pathophysiology are unknown.

5.6.6.2 Clinical Characteristics and Diagnosis

NEH is a rare complication of induction chemotherapy used in the treatment of cancers. In the first report, NEH occurred in the patients with myelogenous leukemia receiving cytarabine [38]. Later, other cancers and other chemotherapeutic agents have been reported to be implicated, as has G-CSF. However, this condition may occur without any association with chemotherapy in patients with leukemia or in HIV-infected patients.

NEH is clinically very similar to SS, and the distinction is usually made by the histopathologic examination. Acute inflammatory plaques usually involve the face or trunk. There is a case report of a patient who developed NEH on three separate occasions provoked by two different chemotherapeutic agents, cytarabine and mitoxantrone. The lesions were morphologically distinct and differed in their anatomical distribution during each episode [39].

Histologically, neutrophils are grouped exclusively around the eccrine secretory coils associated with vacuolar degeneration and necrosis of the secretory

Take Home Message

- RND is an uncommon, but distinctive manifestation of rheumatoid arthritis in general.
epithelium. Sometimes malpighian syringometaplasia or squamous metaplasia occur.

### 5.6.6.3 General Therapeutic Outline

The lesions may resolve after 2–3 weeks.

### 5.6.6.4 Current Established Therapies

No specific therapy is required because the lesions disappear in a few weeks.

### 5.6.6.5 Experimental Approaches

This condition responds to intravenous steroid, but the lesions may recur after their withdrawal [39]. Chronic pruritic NEH in a patient with Behçet’s disease was treated with dapsone 100 mg daily.

#### Take Home Messages

- NEH is a rare, self-limited dermatosis due to chemotherapeutic drugs in most cases.
- Necrosis of the eccrine gland associated with a neutrophilic infiltrate is the histologic hallmark of this disease.

### 5.6.6.6 Global Variation

No variation.

### 5.6.6.7 Pyodermatitis-Pyostomatitis Vegetans

#### Key Features

- Pyodermatitis-pyostomatitis vegetans (PPV), a rare disorder of the skin and oral mucosa, is considered a highly specific marker for IBD, especially UC.
- Flat pustules may be found on mucous membranes.

#### 5.6.6.8 Etiology and Pathophysiology

The etiology and pathophysiology of PPV is unknown, but immunological and psychogenic factors may play a role.

#### 5.6.6.8 Clinical Characteristics and Diagnosis

PPV is a rare disorder of the skin and oral mucosa, although oral lesions (pyostomatitis vegetans) are seen without skin involvement but rarely without gastrointestinal symptoms [40]. PPV is characterized by annular, pustular lesions, which may precede or appear at the same time as the oral lesions. Oral lesions are characterized by multiple pustules on an erythematous base. The friable pustules have a gray to yellow necrotic appearance; they erode and form shallow, “snail-track” ulcers which may affect all areas of oral mucosa, although the most commonly affected sites are the labial and buccal mucosae, hard and soft palate, gingivae, and sulci. The lesions first present as pustules but they later evolve into hyperplastic tissue with a reduction in eosinophils and a predominance of lymphocytes and plasma cells.

A peripheral eosinophilia is observed in 90% of reported cases. Histopathologically, there are intra or subepithelial abscesses containing numerous eosinophils and neutrophils. There may be acanthosis, hyperkeratosis and unusual, reactive multinucleate keratinocytes. The underlying connective tissues contain dense lymphocytic and plasma cell infiltrates. The older lesions show less eosinophilia.

### 5.6.6.10 General Therapeutic Outline

Treatment of PV may be difficult. Management of oral lesions consists mainly of immunosuppression using topical or systemic corticosteroids along with medical and/or surgical treatment of any underlying IBD.

### 5.6.6.11 Current Established Therapies

In the absence of IBD, therapy with topical corticosteroids can be successful, but systemic corticosteroids, dapsone, and sulphasalazine as well as sulphamethoxypyridazine may also be useful. Treatment of any
associated bowel disease, either medically or with colectomy, may be effective in controlling oral and skin lesions.

### 5.6.6.12 Experimental Approaches

No

### 5.6.6.13 Complications to Avoid

Ulcerative colitis.

### Take Home Message

- PPV is a rare oral disorder often associated with gastrointestinal and sometimes with other disorders.

### 5.6.6.14 Global Variation

No variation.

### References

5.7.1 Adult-Onset Still Disease
(Figs. 5.7.1 and 5.7.2)

Key Features

- Cytokines including IL-18 play an important role in the pathogenesis.
- High spiking fever and “rheumatoid rash” are characteristic, although skin manifestations vary.
- NSAID monotherapy is effective only in minority.
- Corticosteroids and DMARDs/immunosuppressants are used in cases resistant to NSAIDs.
- TNF-α inhibitors are potential therapeutic agents effective for the disease.

5.7.1.1 Etiology and Pathophysiology

The etiology and pathogenesis of adult-onset Still disease are unknown. An infection may have a role in the pathogenesis of adult-onset Still disease (AOSD) [1, 2]. Genetic components are also considered important, although inconclusive. HLA-B14, B17, B18, B35, Bw35, Cw4, DR4, Dw6, DR2, and DR7 have been reported to have positive associations while HLA-Bw35 and DR1 have been reported to have negative associations with AOSD [2].

Cytokines play central roles in the pathogenesis of AOSD. They include interferon-gamma (IFN-γ), IL-6, and tumor necrosis factor-alpha (TNF-α) [3]. Th1/Th2
cytokine balance is considered to shift to Th1 in the induction and development of AOSD [4]. Elevated serum levels of the macrophage-colony stimulating factor (M-CSF) in AOSD have also been found in severe, active disease [5]. Over expression of M-CSF may activate the reticulo-endothelial system in AOSD patients and may trigger the sequential cytokine cascade, including IL-6, IFN-γ, and TNF-α.

IL-18 is considered as a pivotal cytokine. IL-18 is overproduced in the acute phase of the disease and is thought to be an upstream initiator of the inflammatory cascade including IFN-γ, IL-6, and TNF-α. Serum IL-18 is elevated in patients with active disease and returns to normal levels after corticosteroid treatment [6]. As for genetic polymorphisms of the human IL-18 gene, the S01/S01 diplotype is a major genetic risk factor for susceptibility to AOSD in a Japanese cohort [7]. IL-18 is produced primarily by activated macrophage-lineage cells, which include Kupffer cells in the liver. Serum IL-18 levels have significantly correlated with serum aminotransferase levels and were a predictor of liver dysfunction in AOSD [8].

5.7.1.2 Clinical Characteristics and Diagnosis

High spiking fevers, typically a single spike, which can continue from 2 weeks to months, are almost always present. The characteristic “rheumatoid rash” is a salmon-pink color, evanescent, urticarial, or measles-like eruption mainly observed on the trunk and extremities. It is usually asymptomatic, but can be pruritic. The rash and fever are often observed simultaneously. Approximately, 80% of patients exhibit arthritis/arthralgia, which can be mild and fleeting, affecting a few joints, or more extensive, although rarely progressively erosive. The common affected joints include knees, wrists, and metacarpophalangeal and proximal interphalangeal joints. Lymphadenopathy and splenomegaly are also often present. Hepatomegaly with serum abnormalities occurs in about 35% of patients. Collectively, with high fever and polyarthritis without joint swelling, the diagnosis is suspected in the presence of the characteristic rash. Infection, malignancies, and other rheumatic diseases need to be ruled out. Increased levels of serum ferritin are the characteristic of the disease. They also exhibit high erythrocyte sedimentation rate, but are negative for rheumatoid factor or antinuclear antibodies. Histological examination reveals a superficial perivascular neutrophilic infiltration without evidence of vasculitis.

5.7.1.3 General Therapeutic Outline

AOSD patients are treated with nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying antirheumatic drugs (DMARDs) and immunosuppressants. Some patients experience adequate control with NSAIDs, while corticosteroids are usually used in those who failed to respond to NSAIDs. Other therapies include parenteral gold, antimalarials, and penicillamine. In some patients whose disease is severely steroid-resistant, immunosuppressants, such as methotrexate (MTX), cyclophosphamide, azathioprine, mechloroethamine, intravenous immunoglobulin, and anti-TNF-α have been used with adequate immediate response.

5.7.1.4 Current Established Therapies

NSAID monotherapy is effective only in 7–15% of cases, and most patients need to be treated with corticosteroids at some point in their disease course with an efficacy of up to 95% [9–11]. The variation in efficacy demonstrated by various studies appears to be related to disease pattern; prednisone was required for 57% of patients with self-limited disease, for 67% with intermittent disease, and for 77% of patients with chronic articular AOSD [12]. Some require corticosteroids only upon a flare of the disease, while others, estimated at approximately half, need maintenance corticosteroid therapy. In those with refractory disease, the efficacy of high-dose intravenous pulse methylprednisolone has also been demonstrated [13].

The third line of therapies consists of DMARDs and immunosuppressants. They are used in cases refractory to the combination of NSAIDs and prednisone. MTX has demonstrated a successful reduction in corticosteroid dose in 85% in a study of 13 patients [14]. Another study of 26 patients demonstrated complete remission in 78%, with 42% discontinuing prednisone altogether, and an overall decrease in daily prednisone by 69% [15]. Treatments other than MTX include cyclosporine A, hydroxychloroquine, gold, penicillamine, azathioprine, and cyclophosphamide.
### 5.7.1.5 Experimental Approaches

Intravenous immunoglobulin (IVIG) has been reported with success rates as high as 87% in the treatment of NSAID-refractory disease [16, 17]. An open-label study of IVIG in early AOSD reported remission in 4 of 7 treated patients [17]. DMARD combination therapy, such as azathioprine + leflunomide [18], or IVIG + mycophenolate mofetil [19], has shown efficacy in cases with refractory disease.

Recent studies have demonstrated utility of the TNF inhibitors such as etanercept, infliximab, and adalimumab in refractory cases [20–25]. IL-6 inhibitor is another promising therapeutic agent targeting cytokine abnormalities. Anti-IL-6 receptor monoclonal antibody has demonstrated a great efficacy in systemic-onset juvenile idiopathic arthritis [26], suggesting a utility in AOSD as well. Several studies have indicated an efficacy of anakinra, a recombinant IL-1 receptor antagonist, in combination with MTX and/or corticosteroids [27, 28]. However, although TNF-α and IL-1 receptor antagonists have been successfully used to control Still’s disease, combinations of both are contraindicated.

Thalidomide has an inhibitory effect against TNF-α production, angiogenesis, cellular adhesion molecule expression, and IL-6 production. There are reports of the successful use of thalidomide (100–200 mg/day) in patients who had failed treatment with corticosteroids and immunosuppressants [29, 30].

### 5.7.1.6 Complications to Avoid

Prolonged corticosteroid administration is often required, and thus various complications with the usage of corticosteroids can occur. In combination therapy using corticosteroids and DMARDS/immunosuppressants, the risk of opportunistic infections significantly increases. Despite the efficacy of anti-TNF therapy, worsening of macrophage activation syndrome in an AOSD patient after initiation of etanercept therapy has been reported [31].

### 5.7.1.7 Global Variations

No global variations have been reported on AOSD.

### 5.7.2 Relapsing Polychondritis

(Fig. 5.7.3)

#### Key Features

- It is an autoimmune disease targeting collagens, matrilin-1, and cartilage oligomeric matrix protein.
- The external ears are most affected with earlobes spared; the nose, the upper respiratory tract, the joints, and the heart are also affected.
- The disease courses are highly variable.
- Systemic corticosteroids are the mainstay of the management.
- Dapsone, azathioprine, cyclophosphamide, MTX, and cyclosporine A are also used.

#### 5.7.2.1 Etiology and Pathophysiology

Relapsing polychondritis (RP) is an autoimmune disease manifesting an autoimmune response that primarily targets the cartilage of the ears, the nose, and the upper respiratory tract exhibiting a chronic relapsing and erosive inflammation [32]. As autoantigens, collagens, matrilin-1, and cartilage oligomeric matrix protein are able to trigger the tissue-specific immune response seen both in patients and in animal models for RP [33, 34].

Like rheumatoid arthritis (RA), RP has been associated with the HLA-DR4 molecule [35, 36]. The serotype HLA-DR4 was found with a significantly higher frequency (50–60%) in RP patients than in healthy controls (25%), and HLA-DR-positive cells were detected in the auricular cartilage from an RP patient with active disease. Furthermore, 30% of RP patients also have other autoimmune diseases, with RA being the most common [37]. These may indicate that shared pathogenic pathways might be used in RP and RA despite the difference in their targets between the joint.

#### Take Home Message

- Treatment of ASOD varies depending on individual patient. Corticosteroids are necessary in most cases, although attempt to minimize the dose should be made.
and the cartilage, which may depend on the difference in autoantigens that initiate or trigger the diseases.

### 5.7.2.2 Clinical Characteristics and Diagnosis

Patients are usually in their 30s–50s. Both sexes are almost equally affected. The most frequent clinical presentation is redness, swelling, and pain in both external ears with ear-lobes spared. The ears ultimately become “floppy” or “cauliflower-like” in appearance.

Joints are often affected as well, but as a nonerosive oligoarthritis or polyarthritis. The nasal involvement is less frequent than the ear, but can result in the characteristic saddle nose deformity. Fever is present in about 40% of the patients. Ocular inflammation includes episcleritis, scleritis, and nongranulomatous uveitis. Respiratory tract involvement, cardiac valvular involvement, and vasculitis of medium and large vessels can also occur. The clinical course of RP is highly variable. It may be punctuated by periodic flares, or may be smoldering, or fulminant with a rapid progressive course. The most frequent causes of death are infection, cardiac failure, and systemic vasculitis [38]. By contrast, spontaneous remissions are also common.

Various other skin manifestations have been described: purpura due to leukocytoclastic or lymphocytic vasculitis, livedo reticularis from leukocytoclastic vasculitis, urticarial papules from leukocytoclastic or lymphocytic vasculitis, bluish-red papules from aseptic neutrophilic infiltrate, erythema elevatum diutinum, nodules on limbs from septal panniculitis, deep neutrophilic infiltrate, vascular thrombosis and leukocytoclastic vasculitis, superficial phlebitis, strele pustules, ulcerations on limbs from thrombosis vessels, leukocytoclastic vasculitis pyoderma gangrenosum-like changes, and distal necrosis [39]. An overlap syndrome of RP and Bechet disease has been described as MAGIC syndrome [40].

Serological studies reveal the presence of antitype II collagen autoantibodies in half of the patients. Other laboratory findings are nonspecific, such as an elevated sedimentation rate, rheumatoid factor, and antinuclear antibodies. Histopathologic examination reveals a loss of basophilia of the cartilage, peripherally damaged chondrocytes, and perichondrial infiltration of inflammatory cells. Granulation tissue and fibrosis are also seen in recurrent or chronic cases.

### 5.7.2.3 General Therapeutic Outline

The highly viable disease course of RP requires individual therapy for optimum management. Although some patients require long-term chronic therapy, others can be treated intermittently. Mild disease may be controlled by such anti-inflammatory drugs as NSAIDs and dapsone. However, in most patients, corticosteroids are the major therapy, which is usually effective in suppressing acute attacks and in controlling and reducing the frequency of recurrence. Immunosuppressants, such as azathioprine, cyclophosphamide, MTX, and cyclosporine A are also used.
5.7.2.4 Current Established Therapies

NSAIDs such as salicylates, naproxen, and indomethacin may be effective in patients with mild symptoms. Dapsone in doses of 25–200 mg/day has been successful in several cases.

Systemic corticosteroids are the mainstay of the management of RP. They improve the acute flares and decrease the frequency and severity of recurrences but may not affect the long-term progression of the disease. Seventy-five patients in McAdam’s series required chronic corticosteroid therapy; the average dose of prednisone was 25 mg/day [37]. Initial doses of oral prednisone range from 30 to 60 mg/day for acute flares, which is subsequently reduced to the lowest possible dose such as 5–10 mg/day. Immunosuppressive therapy, including cyclosporine, azathioprine, and cyclophosphamide, may also be efficacious in several progressive disease, and MTX has been helpful as a steroid-sparing agent. Treatments using hydroxychloroquine, colchicines, penicillamine, and minocycline have been reported. Melphalan, 6-mercaptopurine, and nitrogen mustard are less commonly used nowadays.

Surgical intervention is indicated for certain respiratory and cardiovascular complications [41]. However, surgical treatment of the saddle nose deformity in patients with quiescent disease may result in further collapse and deformity of the septum if disease activity recurs.

5.7.2.5 Experimental Approaches

Other than conventional immunosuppressive drugs, plasmapheresis and anti-CD4 monoclonal antibody therapy have been reported. Successful treatments reported recently include leflunomide [42], mycophenolate mofetil [43], and IL-1 receptor antagonist (anakinra) [44]. Anti-TNF therapy has also been reported as effective [45, 46].

5.7.2.6 Complications to Avoid

The hemoglobin and hematocrit levels need to be monitored for patients on dapsone. The potential risks of the corticosteroid and/or immunosuppressive treatments need to be weighed against potential benefits. The well-known side effects of systemic corticosteroids should always be minimized by the decrease of the dose, although it is often difficult.

5.7.2.7 Global Variations

Caucasians are more frequently affected than the other races.

5.7.3 Reiter Syndrome

5.7.3.1 Etiology and Pathophysiology

A strong association with HLA-B27 has been demonstrated in patients with Reiter disease [47], and the relationship between HLA-B27 and arthritis-causing bacteria have been proposed in the pathogenesis, especially molecular mimicry between HLA-B27 and bacterial molecules. Various bacterial species have been implicated, although these organisms cannot be cultured from the joint fluid or synovium. Nongonococcal Key Features

- There is a strong association with HLA-B27.
- Arthritis, conjunctivitis, and nongonococcal urethritis are the triad.
- Antibiotics are generally ineffective for rheumatic symptoms, and NSAIDs are the first-line treatment.
- Sulfasalazine, corticosteroids, MTX, azathioprine, and cyclosporine are also used.

Take Home Message

- Therapy for optimum management should be considered individually, although full suppression is difficult in progressive cases.
urethritis caused by Chlamydia is the most common sporadic form of Reiter syndrome, while postdysenteric outbreaks have been reported with Shigella, Salmonella, Campylobacter, and Yersinia. Two environmental settings are regularly found: the epidemic or postdysenteric form following infection of the gastrointestinal tract, and the endemic sexually transmitted venereal form following infection of the genitourinary tract. Recent evidence suggests that some bacteria can survive in the synovium in metabolically quiescent states. Some reports have suggested that Reiter syndrome may also occur in association with HIV [48].

5.7.3.2 Clinical Characteristics and Diagnosis

Reiter syndrome is classically defined by the triad of arthritis, conjunctivitis, and nongonococcal urethritis. In most cases, arthritis and conjunctivitis begin within 1–3 weeks of the initial urethritis or diarrhea. The diagnosis can be easily made in such typical cases of a young male with recent sexual exposure and nongonococcal urethritis who suddenly develops the triad. However, clinical courses vary, and the diagnosis in the individual patient is not always easy to confirm.

Involvement of the skin is most common on the palms and soles, but can also be seen on the other regions including mucous membranes. Erythematous papules and macules rapidly develop a vesicopustular or keratotic appearance. Lesions sometimes resemble that of psoriasis. Circinate balanitis is present in about 25% of patients.

Reiter disease is considered among members of seronegative spondyloarthropathies that include ankylosing spondylitis, psoriatic arthritis, Reiter syndrome/reactive arthritis, inflammatory bowel-related arthritis, and undifferentiated spondyloarthropathy. Psoriatic arthritis and Reiter syndrome overlap in several manifestations. Palmoplantar pustulosis may be indistinguishable from “keratoderma blennorrhagicum” but usually does not involve the mucous membranes.

The most important differential diagnosis is gonococcal arthritis, which should be ruled out. An attempt to document a specific bacterial infection should be made, with cultures of the urethra, cervix, synovial fluid, blood, and stool. Nonculture tests are also necessary including direct fluorescent antibody, enzyme-linked immunosorbent assay, and polymerase chain reaction. The presence of HIV should also be tested in those suspected.

Blood examinations reveal an elevated sedimentation rate and an increased C-reactive protein level, with negative rheumatoid factor. HLA examination is useful, often demonstrating HLA-B27, but not in all cases.

5.7.3.3 General Therapeutic Outline

Treatment of rheumatic symptoms in Reiter disease is similar to that of psoriatic arthritis, mainly by NSAIDs. Sulfasalazine and other antirheumatic drugs are used when NSAIDs alone are not fully effective. Antibiotics are generally ineffective, but should be considered in those with active cervicitis or urethritis or with diarrhea.

5.7.3.4 Current Established Therapies

The first-line agents are NSAIDs; when NSAIDs alone are ineffective, sulfasalazine is a useful choice. Occasionally, a short course of corticosteroids may be used, especially after appropriate antibiotics have been completed. In those unresponsive to the above agents, the use of MTX, azathioprine, leflunomide, hydroxychloroquine, and cyclosporine is considered.

5.7.3.5 Experimental Approaches

Recently, anti-TNF-α agents, including etanercept and infliximab, have shown effectiveness in treating Reiter syndrome similar to that shown in psoriatic arthritis [49, 50].

5.7.3.6 Complications to Avoid

Adverse effects of NSAIDs, such as nausea, diarrhea, dizziness, drowsiness, edema, kidney failure, liver failure, and gastric ulcers, should be noticed.
In contrast to the effectiveness of anti-TNF-α, a report has described Reiter syndrome triggered by adalimumab and leflunomide in a patient with ankylosing spondylarthropathy and Crohn disease [51].

### Take Home Message

- Reiter disease is a form of seronegative reactive arthritis triggered by bacterial infection on a genetic susceptibility, and shares some characteristics with psoriatic arthritis including treatment.

### 5.7.3.7 Global Variations

Its worldwide occurrence appears to relate to the prevalence of HLA-B27 in each population. HLA-B27 is positive in 0.2% of Caucasians, while it is only 0.04% in Japanese.

### References

Part VI

Acne and Rosacea
6.1    Introduction

Acne vulgaris is the most common skin disease with a prevalence of approximately 85% in adolescent and young adult ages [1, 2]. It is characterized by clinically noninflammatory follicular papules called comedones, and by additional inflammatory papules, pustules, and nodules in its more severe forms. Acne vulgaris affects areas of skin with the densest population of sebaceous follicles; these areas include the face, the upper part of the chest, and the back [3–5]. For most patients, acne represents a bothersome problem; however, in severe cases, excessive host inflammatory response can result in painful nodules and disfiguring scars that affect adolescent’s self image and may lead to depression and social isolation [6].

6.1.2 Etiology and Pathophysiology

The pathogenesis of acne vulgaris is multifactorial. According to the classical concept, four key factors are responsible for the development of acne lesions,
namely, follicular epidermal hyperproliferation with subsequent plugging of the follicle, excess sebum production due to sebaceous gland hyperplasia, colonization, and activity of *Propionibacterium acnes*, as well as host immune response and inflammation. Follicular epidermal hyperproliferation and excess sebum production can induce microcomedone a preclinical acne lesion, to proceed to comedone (closed or open) or further to papule, pustule, or nodule [7, 8].

Follicular epidermal hyperproliferation is the first recognized event in the development of acne. The exact underlying cause of this hyperproliferation is still unknown. Comedones arise due to the accumulation of abnormally desquamated keratinocytes in the sebaceous follicles [7]. Currently, three leading hypotheses have been proposed to explain the follicular epithelium hyperproliferation in individuals with acne. First, androgen hormones are believed to be the initial trigger. Comedones begin to appear around adrenarche and the degree of comedonal acne in prepubertal girls correlates with circulating levels of the adrenal androgen dehydroepiandrosterone sulfate (DHEA-S) [9]. Furthermore, androgen hormone receptors are present in the portion of the follicle where the comedone forms; individuals with malfunctioning androgen receptors do not develop acne [10–12]. Second, acne patients frequently have oily skin due to increase in size of sebaceous follicles and number of lobules per gland [4]. This excess sebum may dilute the normal epidermal lipids and hence a change occurs in the relative concentrations of the various lipids. It has been suggested that comedone formation is initiated by a relative decrease in linoleic acid as a result of dilution by excess sebum [13]. Third, inflammation can be produced by invading CD4 T cells [14].

Excess sebum is another key factor in the development of acne vulgaris. Sebum production and excretion are regulated by a number of different hormones and mediators. Androgen hormones, in particular, promote sebum production and release; however, most men and women with acne have normal circulating levels of androgen hormones. An end-organ hyperresponsiveness to androgen hormones has been hypothesized. Androgen hormones are not the only regulators of the human sebaceous gland [15]. Numerous other agents, including growth hormone and insulin-like growth factor, also regulate the sebaceous gland and may contribute to the development of acne [15–17].

*P. acnes* are a microaerophilic organism that has not been shown to be present both in normal skin and in the early lesions of acne, but its presence in later lesions is almost certain. *P. acnes* may stimulate inflammation by producing proinflammatory mediators that diffuse through the follicle wall [18]. Recent studies have shown that *P. acnes* bind to the Toll-like receptor 2 on monocytes and neutrophils. Binding of the Toll-like receptor 2 then leads to the production of multiple proinflammatory cytokines, including IL-12, IL-8, and tumor necrosis factor. Hypersensitivity to *P. acnes* may also explain why some individuals develop inflammatory acne vulgaris while others do not [19, 20].

Inflammation may be a primary or a secondary phenomenon. Most of the evidence to date suggests a secondary inflammatory response to *P. acnes* as already mentioned. However, IL-1α expression has been identified in the microcomedone, and it may play a role in the development of comedones [16, 21]. Zouboulis suggested that the pilosebaceous gland itself might be the origin of proinflammatory mediators, such as free fatty acids in sebum [22]. Ex vivo and in vitro studies demonstrated that IL-1α can be synthesized by sebocytes and follicular keratinocytes without the presence of microorganisms and that *P. acnes* are not able to induce IL-1α expression [23, 24].

On the other hand, ongoing research is modifying the classical view of acne pathogenesis through identification of up-stream mechanisms leading to the phenotypic and laboratory findings detected in acne. Androgens, skin lipids, inflammatory signaling and regulatory neuropeptides [25] seem to be mainly involved in this multifactorial process [16]. Also, there is increasing evidence that hereditary factors play an important but indirect role in acne.

### 6.1.3 Clinical Characteristics and Diagnosis

Local symptoms in acne may include pain or tenderness. Systemic symptoms are generally absent in acne vulgaris. The rarely occurring severe acne with associated systemic signs and symptoms is referred to as acne fulminans. Acne may have a psychological impact on any patient, regardless of the severity or the grade of the disease.
361

6.1 Acne and Its Variants

Acne vulgaris is characterized by comedones, papules, pustules, and nodules in a sebaceous distribution. A comedone can present as closed (whitehead) or open (blackhead) without clinical signs of inflammation. Papules and pustules are raised lesions with obvious inflammation. The face may be the only involved skin surface, but the chest, the back, and the upper arms are often involved.

In comedonal acne, only a few inflammatory lesions can be present. Comedonal lesions are the earliest lesions of acne, and closed comedone is the precursor lesion of inflammatory lesions. Mild inflammatory acne is characterized by inflammatory papules and comedones. Moderate inflammatory acne has comedones, inflammatory papules and pustules. Greater numbers of lesions are present than in milder inflammatory acne. Nodulocystic acne is characterized by comedones, inflammatory lesions, and large nodules greater than 5 mm in diameter. Scarring is often evident.

Inflammatory lesions and areas that have been traumatized often heal with residual erythema or pigmented change that may persist for months after the initial acne lesions have cleared. Permanent scarring can also occur, especially with larger inflammatory lesions. The most common permanent scarring is the “ice-pick” variety that occurs on the cheeks.

Acne is currently classified into three grades based on its severity and six subgrades according to the predominant type of lesions [26] (Fig. 6.1.1):

- Grade 1 mild Comedonal Papulopustular
- Grade 2 moderate Papulopustular Nodular
- Grade 3 severe nodulocystic Conglobate

An external cause is seldom identifiable in acne vulgaris. Some cosmetic agents and hair pomades may worsen acne [27, 28]. Medications that can promote acne include steroids, lithium, some antiepileptics, and iodides [5]. Congenital adrenal hyperplasia, polycystic ovary syndrome, and other endocrine disorders with excess androgens may trigger the development of acne vulgaris. Acne vulgaris may also be influenced by genetic factors.

In a female patient with dysmenorrhea or hirsutism, a hormonal evaluation should be considered. Patients with evidence of virilization must have their total testosterone levels measured. Many authorities would also measure free testosterone, DHEA-S, leuteinizing hormone, follicle-stimulating hormone and prolactin levels [29]. Skin lesion cultures to rule out gram-negative folliculitis are warranted when no response to treatment occurs or when improvement is not maintained.

6.1.4 Acne Variants and Syndromes

Acne conglobata is a severe form of acne characterized by burrowing and interconnecting abscess and often scarring, both keloidal and atrophic. Comedones occur in a group of 2 or 3 and cysts contain foul smelling seropurulent material. The lesions are usually present on the chest, shoulders, back, buttocks, upper arms and thighs and face.

Acne fulminans is an extremely severe cystic acne commonly associated with fever and leukocytosis and polyarthralgia, polymyalgia, destructive arthritis, and myopathy [30, 31].

Preadolescent acne may occur as neonatal, or infantile or childhood acne. Neonatal acne is a common condition occurring in the first 4 weeks after birth and results from circulating maternal hormones. It develops shortly after birth, has a male sex preponderance and is characterized by facial papules or pustules that clears spontaneously in a few days or weeks [32]. Infantile acne includes cases that persist beyond the neonatal period and childhood acne may evolve from persistent infantile acne or begin after 2 years of age. Both conditions are uncommon and have a male predominance. There is a strong family history of severe acne, whereas a correlation of neonatal acne and familial hyperandrogenism has been detected [33, 34].

Acne occurs or persists in 8% of the adults over the age of 25 years and even in 3% over the age of 35 years (acne tarda) [5, 32]. Acne tarda is prevalent mostly in females (females : males; 5:1). DHEA-S may be responsible for acne tarda in females, which also present with inflammatory lesions of the lower part of the face [29]. In 50% of the cases with acne tarda a familial occurrence of acne can be registered.

Tropical acne is characterized by severe nodular, cystic and pustular lesions occurring on the back, buttocks, and thighs in the tropics during the hot and humid seasons. Comedones are sparse and the face is characteristically spared.
Acne venenata is due to exposure to comedogenic chemicals with extensive formation of comedones. Chlorinated hydrocarbons (chloracne), cutting oils, petroleum oil, and coal tar and pitches are the most commonly encountered occupational settings [27, 35].

Acne cosmetica is a persistent low grade acne manifested by closed comedones and papulopustules commonly seen in middle aged women on the cheeks and chin and is due to acnegenic cosmetics. The condition is uncommon due to the widespread use of low and noncomedogenic products [27, 36]. Pomade acne is a variety of cosmetic acne occurring exclusively in blacks applying various greases and oils to scalp hair. The lesions are usually closed comedones on the forehead, temples, cheeks, and chin [37].

<table>
<thead>
<tr>
<th>Classification</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Acne fulminans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comedonic</td>
<td>tretinoin 0.1% cream</td>
<td>doxycycline 2x100 mg/d po</td>
<td>isotretinoin 0.5 mg/kg/d po</td>
<td>prednisolone 3x10 mg – isotretinoin 0.5 mg/kg/d po</td>
</tr>
<tr>
<td>Papulopustular</td>
<td>benzoyl peroxide 5% gel</td>
<td>cyclopenterone acetate 2 mg - ethinyl estradiol 35µg/d po</td>
<td>isotretinoin 1 mg/kg/d po</td>
<td></td>
</tr>
<tr>
<td>Nodular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conglobate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 6.1.1** Classification of acne vulgaris and acne fulminans with therapeutic results
6.1 Acne and Its Variants

The SAPHO syndrome is characterized by synovitis, acne (acne fulminans or acne conglobata), pustulosis, hyperostosis, and osteomyelitis, with acne lesions mostly on the chest wall. AHYS is acquired hyperostosis syndrome with severe acne similar to that of SAPHO syndrome [38, 39].

6.1.5 General Therapeutic Outlines

There are many myths surrounding acne and it is important to educate patients and emphasize that acne is neither due to infections nor is it infectious to others and is not due to poor hygiene. Whether acne is related to diet is still unclear and remains a controversial issue. Recent nutritional studies related acne severity with high glycemic load diet (15% energy from protein, 55% energy from carbohydrate) and milk consumption [40, 41], a view that was not supported by others [42]. The authors of these studies admitted that several confounding factors were not eliminated and may have biased the results. Despite the ease and availability of nutritional studies, the issue of acne and diet has not been resolved and no conclusive data are available over the last decades.

Acne may worsen a week before menses in adult females (premenstrual flare). Both males and females with acne should be advised against picking at lesions [26].

Patients should be instructed to treat their skin gently. Mild, nonabrasive cleansers and non comedogenic moisturizers and cosmetics are preferred in case the patients insist; however, a general advice against any manipulations of the skin must be provided. In this context, washing the face with running water may be optimal. In general, gel based products and preparations containing silicone derivatives (cyclomethicone, dimethicone) are less comedogenic than lotions and oil based products. Cosmetics should improve skin appearance by minimizing erythema and providing adequate camouflage. Prescriptions of cleansers and other active and specific anti-acne pharmaceutical preparations should also be accompanied by a discussion of the potential adverse effects [43].

Treatment is directed toward the known pathogenic factors involved in acne. This include correcting altered follicular keratinization, decreasing androgenic effects, reducing sebum production or better reducing the amount of proinflammatory lipids in sebum, and modulating the host response. Inhibiting growth of *P. acnes* is still considered a therapeutic target of acne by a number of clinicians. The grade and the severity of the acne help in determining which of the following treatments, alone or in combination, is most appropriate.

1. Follicular keratinisation is corrected by topical retinoids and oral isotretinoin, with the latter being the most potent anti-acne compound since it is active against all pathogenetic factors of the disease. Topical azelaic acid may also help in normalizing disturbed keratinisation and keratolytics dissolve the hyperkeratotic follicular plug. Although comedones can also be physically extracted, mechanically expressed or lightly cauterized, these mechanical treatments are not recommended since they can lead easily to scar development.

2. Androgen effects can be controlled only in females. Effective compounds are antiandrogenic oral contraceptives; these have especially been active as androgen receptor blockers, such as cyproterone acetate, chloromadinone acetate, drospirenone as well as spironolactone and eventually flutamide [44, 45].

3. Reduction of sebum production by oral isotretinoin and antiandrogen/estrogen combinations in females [44–46].

4. Modulation of host inflammatory response by topical and systemic antibiotics with a paraantiinflammatory activity. Those are the family of tetracyclines, retinoids, benzoyl peroxide and azelaic acid as well as intraleral injection or in selected cases a short course of systemic glucocorticoids, as in acne fulminans.

5. Inhibition of growth of *P. acnes* by topical benzoyl peroxide and azelaic acid and topical and systemic antibiotics may be of advantage.

6.1.6 Currently Established Therapies

Effective treatment is rarely possible with a single agent; more commonly multiple agents are combined in the treatment of this multifactorial condition. The combination of different classes is based on the
Clinical grade of acne. A treatment algorithm for acne is given in Table 6.1.1.

Topical retinoids, such as tretinoin, isotretinoin, motretinide, adapalene, and tazarotene correct altered follicular keratinisation [47] (Table 6.1.2; Fig. 6.1.1). They are comedolytic and have anti-inflammatory effect. They induce epidermal differentiation and, thus, normalize follicular hyperproliferation and hyperkeratinization. Topical retinoids reduce the number of microcomedones, comedones, and inflammatory lesions. They may be used alone or in combination with other acne medications. Tretinoin is available as gel (0.01 and 0.025%), cream (0.025, 0.05 and 0.1%), and liquid (0.025%). Adapalene 0.1% is also available as cream, gel and solution, all with similar efficacy. Tazarotene is available as 0.1% cream or gel. Cutaneous erythema, peeling, and edema with tretinoin are dose-related side effects. Adapalene is less likely to cause skin irritation and is better tolerated than tretinoin or tazarotene, but tazarotene appears to be the most efficacious [48, 49]. Retinoids are applied once daily to clean, dry skin, but they may need to be applied less frequently if irritation occurs. The use of mild, nondrying cleansers and noncomedogenic moisturizers may help reduce the irritation and peeling. Alternate-day dosing may be used if irritation persists. Short-contact therapy starting with 30 s and building up to 1 h or more followed by washing is effective and safe.

### Table 6.1.1 Treatment algorithm for acne (modified from ref. [26])

<table>
<thead>
<tr>
<th>Mild acne</th>
<th>Comedonal</th>
<th>Topical retinoid</th>
<th>Or</th>
<th>Maintenance with topical retinoid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other topical retinoid</td>
<td>Or maintenance with a topical retinoid and benzoyl peroxide</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Azelaic acid</td>
<td>Females: hormonal treatment and topical retinoid±benzoyl peroxide</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ο-α-Hydroxy acid</td>
<td>Females: hormonal treatment and topical retinoid±oral antibiotic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>β-Hydroxy acid</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Salicylic acid</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Combinations</td>
<td></td>
</tr>
<tr>
<td>Papulopustular acne</td>
<td>Topical retinoid and benzoyl peroxide</td>
<td>Or</td>
<td>Topical retinoid and topical antibiotic</td>
<td>Maintenance with topical retinoid ± benzoyl peroxide</td>
</tr>
<tr>
<td>Moderate acne</td>
<td>Papulopustular acne</td>
<td>Oral antibiotic and topical retinoid±benzoyl peroxide</td>
<td>Or</td>
<td>Oral antibiotic and topical retinoid±benzoyl peroxide</td>
</tr>
<tr>
<td>Nodular acne</td>
<td>Oral antibiotic and topical retinoid ± benzoyl peroxide</td>
<td>Or</td>
<td>Oral isotretinoin</td>
<td>Maintenance with topical retinoid ± benzoyl peroxide</td>
</tr>
<tr>
<td>Severe acne</td>
<td>Nodulocystic/conglobate acne</td>
<td>Oral isotretinoin</td>
<td>Oral antibiotic and topical retinoid ± benzoyl peroxide</td>
<td>Maintenance with topical retinoid ± benzoyl peroxide</td>
</tr>
</tbody>
</table>

### Table 6.1.2 Evidence-based topical retinoid treatment (from ref. [49])

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adapalene 0.1% cream</td>
<td>&gt; Placebo</td>
</tr>
<tr>
<td>Tazarotene 0.1% gel</td>
<td>&gt; Placebo</td>
</tr>
<tr>
<td>Adapalene 0.1% gel</td>
<td>= Tretinoin 0.05% gel</td>
</tr>
<tr>
<td>Tazarotene 0.1% gel</td>
<td>&gt; Tretinoin 0.1% gel</td>
</tr>
<tr>
<td>Tazarotene 0.1% gel</td>
<td>&gt; Tretinoin 0.025% gel</td>
</tr>
<tr>
<td>Tazarotene 0.1% gel</td>
<td>&gt; Adapalene 0.1% gel</td>
</tr>
<tr>
<td>Tazarotene 0.1% gel 1×/2 day</td>
<td>= Adapalene gel 0.1% gel 1×/day</td>
</tr>
<tr>
<td>Motretinide 0.1% cream</td>
<td>= Benzoyl peroxide 5% gel</td>
</tr>
</tbody>
</table>

Topical antimicrobials are mainly used for their anti-inflammatory activity and role against *P. acnes* (Table 6.1.3, Fig. 6.1.1). Currently available topical antimicrobials include benzoyl peroxide, clindamycin, erythromycin, tetracycline, and in addition, azelaic acid, which has demonstrated antibacterial activity against *P. acnes* [51].

Benzoyl peroxide is effective through creation of superoxide state that is not tolerated by *P. acnes*, and bacterial resistance to benzoyl peroxide has not been reported. Benzoyl peroxide is available in a variety of topical forms, including soaps, washes, lotions, creams, and gels [52]. Benzoyl peroxide may be used once or twice a day. It bleaches hair, clothes and bed linens. It may (rarely) cause a true allergic contact dermatitis but, more often, an irritant contact dermatitis develops especially if benzoyl peroxide is used with tretinoin or when accompanied by aggressive washing methods [53].

Topical antibiotics such as clindamycin, erythromycin and sulfacetamide are commonly used due to their

<table>
<thead>
<tr>
<th>Table 6.1.3 Evidence-based topical treatment with benzoyl peroxide, antibiotics, azelaic acid and combinations (from refs. [49, 98])</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzoyl peroxide (BPO)</strong></td>
</tr>
<tr>
<td><strong>Clindamycin</strong></td>
</tr>
<tr>
<td><strong>Erythromycin 2%</strong></td>
</tr>
<tr>
<td><strong>1.5% solution</strong></td>
</tr>
<tr>
<td><strong>Nadifloxacin 1% cream</strong></td>
</tr>
<tr>
<td><strong>BPO 5% gel</strong></td>
</tr>
<tr>
<td><strong>BPO</strong></td>
</tr>
<tr>
<td><strong>Clindamycin 1% gel</strong></td>
</tr>
<tr>
<td><strong>Clindamycin</strong></td>
</tr>
<tr>
<td><strong>Clindamycin 1%/BPO 5% gel</strong></td>
</tr>
<tr>
<td><strong>Clindamycin/BPO</strong></td>
</tr>
<tr>
<td><strong>Erythromycin/BPO</strong></td>
</tr>
<tr>
<td><strong>Erythromycin/BPO</strong></td>
</tr>
<tr>
<td><strong>Erythromycin/BPO</strong></td>
</tr>
<tr>
<td><strong>Erythromycin 4%/zinc solution</strong></td>
</tr>
<tr>
<td><strong>Adapalene 0.1%/clindamycin 1% gel</strong></td>
</tr>
<tr>
<td><strong>Adapalene 0.1% gel/Lymecyclin po (300 mg/day)</strong></td>
</tr>
<tr>
<td><strong>Tretinoin/clindamycin gel</strong></td>
</tr>
<tr>
<td><strong>Tretinoin/erythromycin</strong></td>
</tr>
<tr>
<td><strong>Azelaic acid 20% cream</strong></td>
</tr>
<tr>
<td><strong>Azelaic acid 15% gel</strong></td>
</tr>
<tr>
<td><strong>Azelaic acid 15% gel</strong></td>
</tr>
</tbody>
</table>
bacteriostatic effect against \textit{P. acnes}. They are not comedolytic, and bacterial resistance may develop to any of these agents. The development of resistance is lessened if topical antibiotics are used in combination with benzoyl peroxide and these combinations have been shown to have better results than each drug alone [54]. Commonly prescribed topical antibiotics include erythromycin and clindamycin alone or in combination with benzoyl peroxide. Clindamycin and erythromycin are available in a variety of topical agents. They may be applied once or twice a day. Gels and solutions may be more irritating than creams or lotions. Combining topical antibiotics with topical retinoids, such as clindamycin 1% plus adapalene gel 0.1% or tretinoin with either erythromycin or clindamycin showed favorable response in inflammatory and noninflammatory lesions [49]. Adverse effects of topical antibiotics include erythema, peeling, dryness, and burning. Currently it is recommended that topical antibiotics should not be used alone due to the potential for bacterial resistance and relatively slow onset of action [26].

The antibacterial agent azelaic acid 20% is also effective in correcting keratinization. Azelaic acid also inhibits bacterial protein synthesis through an unclear mechanism. Clinical trials have shown equal efficacy to topical antimicrobials and tretinoin [51]; a finding that has not been appreciated by other experts.

### 6.1.7 Systemic Treatments

Systemic antibiotics are a mainstay in the treatment of acne vulgaris [55, 56] (Table 6.1.4, Fig. 6.1.1). These agents have both antimicrobial and anti-inflammatory properties. Depending on the dose administered, they inhibit inflammatory processes [16] as well as reduce \textit{P. acnes} within follicles, thereby supposed to inhibit production of bacterial-induced inflammatory cytokines [18]. The tetracycline group of antibiotics is commonly prescribed for acne. In contrast to doxycycline and minocycline, tetracycline must not be taken with dairy products as its absorption is reduced. Minocycline (50–100 mg twice daily), as the more lipophilic compound, is supposed to be more effective than tetracycline (500 mg twice daily) or doxycycline (50–100 mg twice daily) by those proposing the antibacterial effect as the most important anti-acne one. Greater efficacy may also be due to less \textit{P. acnes} resistance to minocycline [57], the newest of the classical tetracyclines. However, \textit{P. acnes} resistance is becoming more common with all classes of antibiotics currently used to treat acne vulgaris, except the less used new ones, azithromycin (250 mg twice daily) and limecycline (150 mg twice daily). Bacterial resistance to these systemic agents may be reduced by combining them with topical retinoids and/or topical benzoyl peroxide [58]. Despite the high rates of \textit{P. acnes} resistance to erythromycin worldwide, the compound is further widely used in the treatment of acne with success, and another argument that the anti-inflammatory effect and not the antibiotic one is what is important in acne treatment. Therefore, low dose antibiotics (under the minimal inhibitory dose) such as doxycycline (20 mg twice daily), azithromycin (500 mg once or thrice weekly) or limecycline (150 mg daily) with an additional advantage of not inducing bacterial resistance are currently prescribed. Other antibiotics, such as clindamycin and trimethoprim/sulfa-methoxazole are second line treatments.

Oral isotretinoin is the only compound that is active against all pathogenetic factors of acne, by decreasing sebum secretion, correcting keratinisation and reducing inflammation [59–61] (Table 6.1.5, Fig. 6.1.1). The reduction of sebum secretion is due to inhibition of sebaceous gland differentiation and proliferation and reduction of sebaceous gland size [46]. It is highly effective in the treatment of severe, recalcitrant acne vulgaris, however, because of the significant adverse effects, it should be reserved for patients who are unresponsive to conventional therapy including systemic antibiotics [62]. Isotretinoin therapy should be at a dose of 0.5 mg/kg/day, and reduced if not tolerated, until achieving a

<table>
<thead>
<tr>
<th>Table 6.1.4 Evidence-based systemic treatment with oral antibiotic (from refs. [49, 98, 99])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracycline &gt; Placebo</td>
</tr>
<tr>
<td>Doxycycline (&lt;MIC dose) &gt; Placebo</td>
</tr>
<tr>
<td>Minocycline &gt; Placebo</td>
</tr>
<tr>
<td>Limecycline (300–150 mg/day) &gt; Placebo</td>
</tr>
<tr>
<td>Tetracycline = Erythromycin</td>
</tr>
<tr>
<td>Oxytetracycline = Minocycline</td>
</tr>
<tr>
<td>Minocycline = Lymecycline</td>
</tr>
<tr>
<td>Tetracycline &gt; Zinc glukonate</td>
</tr>
<tr>
<td>Oxytetracycline = Zinc glukonate</td>
</tr>
<tr>
<td>Azithromycin (500 mg/day 1–3 day/week) = Doxycycline (daily)</td>
</tr>
</tbody>
</table>

C. C. Zouboulis and M. B. Abdel-Naser
good clinical effect (over 4–12 months). Greater treatment failures and higher relapse rates were observed with lower doses (0.1 mg/kg/day) and with a cumulative dose of less than 120 mg/kg [63]. Coadministration with topical steroids at the onset of therapy (3–4 weeks) may be useful in severe cases to prevent the occurrence of initial worsening. Systemic isotretinoin, like all systemic retinoids, is a teratogen mandating strict precautions for use among women of childbearing age [62]. Associated mood changes and depression have been reported during treatment. Although the cause is not clear, patients should be informed of this potential side effect and must sign a consent form acknowledging that they are aware of this potential risk.

Several hormonal therapies may be effective in the treatment of acne vulgaris in females [44] (Table 6.1.6, Fig. 6.1.1). Oral contraceptives containing 35 mg ethinyl estradiol or less increase the levels of sex hormone binding globulin, resulting in an overall decrease in circulating free testosterone. Of the several gestagens administered, cyproterone acetate, chlormadinone acetate, and drospirenone seems to be the most effective in acne [44]. A combiphasic preparation with desogestrel/ethinyl estradiol also seems to be a potent anti-acne drug [49]. Spironolactone (50–100 mg/day) may also be useful in the treatment of acne vulgaris as an adjuvant therapy. Adverse effects of spironolactone include dizziness, breast tenderness, and dysmenorrhea. Dysmenorrhea may be lessened by coadministration with an oral contraceptive. Periodic evaluation of blood pressure and potassium level is appropriate. Pregnancy must be avoided while on spironolactone because of the risk of feminization of the male fetus. Flutamide (250–500 mg/day) is used in women with hirsutism and acne.

**Table 6.1.5** Evidence-based systemic treatment with isotretinoin (from refs. [49, 100])

<table>
<thead>
<tr>
<th>Isotretinoin</th>
<th>&gt;</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isotretinoin 1 mg/kg/day</td>
<td>=</td>
<td>Isotretinoin 0.5 mg/kg/day</td>
</tr>
<tr>
<td>Isotretinoin 0.5–1 mg/kg/day</td>
<td>&gt;</td>
<td>Isotretinoin 0.1 mg/kg/day</td>
</tr>
<tr>
<td>Isotretinoin 1 mg/kg/day</td>
<td>=</td>
<td>Micronised isotretinoin 0.4 mg/kg/day</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>&gt;</td>
<td>Cyproterone acetate/ethinyl estradiol</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>&gt;</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>&gt;</td>
<td>Dapsone</td>
</tr>
</tbody>
</table>

**Table 6.1.6** Evidence-based systemic treatment with anti-androgens (from ref. [44, 49])

<table>
<thead>
<tr>
<th>Cyproteroneacetat (2 mg) / Ethinylestradiol (35 µg)</th>
<th>&gt;</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dienogest (3 mg) / Ethinylestradiol (30 µg)</td>
<td>&gt;</td>
<td>Placebo</td>
</tr>
<tr>
<td>Norgestimate/ethinyl estradiol</td>
<td>&gt;</td>
<td>Placebo</td>
</tr>
<tr>
<td>Levonogestrel/ethinyl estradiol</td>
<td>&gt;</td>
<td>Placebo</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>&gt;</td>
<td>Placebo</td>
</tr>
<tr>
<td>Cyproterone acetate/ethinyl estradiol</td>
<td>=</td>
<td>Drospirenone/ethinyl estradiol</td>
</tr>
<tr>
<td>Cyproterone acetate/ethinyl estradiol</td>
<td>=</td>
<td>Combiphasic preparation with desogestrel/ethinyl estradiol</td>
</tr>
<tr>
<td>Cyproterone acetate (2 mg)/ethinyl estradiol (35 µg)</td>
<td>=</td>
<td>Dienogest (3 mg)/ethinyl estradiol (30 µg)</td>
</tr>
<tr>
<td>Cyproterone acetate/ethinyl estradiol</td>
<td>&gt;</td>
<td>Desogestrel/ethinyl estradiol</td>
</tr>
<tr>
<td>Cyproterone acetate/ethinyl estradiol</td>
<td>&gt;</td>
<td>Levonogestrel/ethinyl estradiol</td>
</tr>
<tr>
<td>Cyproterone acetate/ethinyl estradiol</td>
<td>&gt;</td>
<td>Flutamide</td>
</tr>
<tr>
<td>Chlormadinone acetate/ethinyl estradiol</td>
<td>&gt;</td>
<td>Levonogestrel/ethinyl estradiol</td>
</tr>
<tr>
<td>Drospirenone/ethinyl estradiol</td>
<td>&gt;</td>
<td>Norgestimate/ethinyl estradiol</td>
</tr>
<tr>
<td>Desogestrel/ethinyl estradiol</td>
<td>&gt;</td>
<td>Levonogestrel/ethinyl estradiol</td>
</tr>
<tr>
<td>Desogestrel/ethinyl estradiol</td>
<td>&gt;</td>
<td>Gestodene</td>
</tr>
<tr>
<td>Levonogestrel/ethinyl estradiol</td>
<td>=</td>
<td>Norethindrone acetate/ethinyl estradiol</td>
</tr>
</tbody>
</table>

Therapy of choice for acne conglobata and acne fulminans (Fig. 6.1.1) is isotretinoin (0.5 mg/kg) for 4–12 months in combination with systemic steroids such as prednisolone (10 mg thrice daily) for 3–4 weeks particularly in the presence of systemic symptoms. Oral tetracycline (500 mg 4 times daily) or erythromycin (1 g twice daily) are alternatives. Resistant cases can be treated with dapsone (50–150 mg daily) [64].

In selected cases manual extraction of comedones and electrocauterization of comedones and pustules under EMLA cream have shown to be useful as a topical anesthetic. Additionally, some patients may benefit...
from superficial peels with \( \alpha \)-hydroxy acid (30–70%) or salicylic acid (1–5%) in \( \beta \)-hydroxy acid [43]. However, mechanical manipulation of acne lesions can also induce acne scars and, therefore, has to be applied carefully.

Additional measures may be helpful in bringing quick resolution of the cysts. Aspiration, intralesional injection of triamcinolone acetonide at doses of 0.75–2.5 mg/mL diluted in sterile normal saline solution [65], cryotherapy, and occasionally, surgical excision of the interconnecting large nodules can be deployed for rapid cosmetic improvement.

### 6.1.8 Complications to Avoid

Acne lesions may lead to permanent scarring, which is the major rational for treatment of this non fatal condition. Treating acne during pregnancy is a challenge. Many of the most commonly prescribed acne medications are not safe during pregnancy. A safer approach incorporates topical or systemic erythromycin or clindamycin. Tetracyclines can cause gastrointestinal upset and vaginal candidiasis in females. In children younger than 10 years, tetracycline can cause enamel hypoplasia and yellowish discoloration of forming teeth. Doxycycline can cause photosensitivity and minocycline vertigo, dizziness, ataxia, rarely bluish discoloration of skin, and an autoimmune syndrome, with drug induced lupus erythematoses, autoimmune hepatitis, and hypersensitivity syndrome [75, 94]. The presence of these side effects is an indication for a shift to doxycycline or erythromycin, even if some authors still associate the high rates of bacterial resistance to erythromycin with therapeutic failure [77, 78]. Antibiotic resistance can be avoided by short term use of systemic antibiotics when feasible. Baseline assessment of antinuclear antibody levels and hepatic transaminases has been recommended for patients expected to be on minocycline for more than 1 year. Blood cell counts should be obtained and monitored in patients on trimethoprime or trimethoprim/sulfamethoxazole.

Isotretinoin is a teratogen (category X), and pregnancy under isotretinoin must be avoided. Contraception counseling is mandatory, and two negative pregnancy test results are required prior to the initiation of therapy [62]. Contraception, preferably by two different forms is given 1 month before starting therapy, while taking it, and for 1 month after it has been discontinued. Patients should not donate blood during therapy and for one month following its discontinuation, as blood might be given to a pregnant woman. Baseline laboratory examination should also include cholesterol and triglyceride assessment, hepatic transaminases, and a complete blood count. Pregnancy tests and laboratory examinations should be repeated monthly during treatment. The patient is considered at high risk for abnormal healing and development of excessive granulation tissue following surgical procedures. Many dermatologists delay elective procedures, such as dermabrasion or laser resurfacing, for up to a year after completion of systemic isotretinoin therapy. Other procedures to be avoided during therapy include tattooing, piercing, leg waxing, and other epilation procedures during therapy and at least 6 months following cessation of treatment. Dry lips, dry skin, dry eyes that can be lessened by emollients, and decreased night vision, headache, epistaxis and backache may occur [47, 49, 59]. Evidence for an association between isotretinoin and depression is lacking, nevertheless patients and their relatives must be informed about depressive symptoms and screening for depression should be an essential part of each visit [79].

Appropriate laboratory examinations (electrolytes with particular attention to potassium levels and, when appropriate, pregnancy tests) should be ordered as baseline and in follow up when spironolactone is prescribed.

### 6.1.9 Acneiform Dermatoses

Rosacea (is described in detail in Chap. 6.2).

Folliculitis due to gram-negative bacteria or pityrosorum ovale typically presents as erythematous, pruritic follicular papules or pustules that may occur on the trunk and extremities. Treatment of folliculitis is directed toward avoidance of precipitating factors such as occlusion, excessive sweating, and prolonged immersion in water. Appropriate antimicrobial therapy, if needed, should be chosen after culture results have been obtained for bacteria, fungus and mites [66, 67]. In gram-negative folliculitis, culture usually reveals entrobacter and klebsiella or proteus from deep cystic lesions. The condition is commonly seen in acne patients who have been treated with long-term antibiotics mainly tetracyclines. Specific topical or systemic treatment to treat the etiologic agent or isotretinoin in severe cases is the treatment of choice [68].
Steroid-induced acne is a complication of topical and systemic corticosteroids, which is characterized by abrupt onset of pruritic monomorphic papules or pustules affecting primarily the upper trunk, 2–6 weeks after initiating the administration of corticosteroids. Comedones are generally absent in steroid-induced acne. The condition resolves with discontinuation of the corticosteroids. Treatment with topical or systemic retinoids may be helpful even if the steroids are continued, whereas topical antibiotics and benzoyl peroxide may be less beneficial [69, 70].

Seborrheic dermatitis is a chronic dermatosis involving the seborrheic (oily) areas that is easy to diagnose. Rarely, papules and pustules that resemble acne may arise, often following prolonged use or abrupt cessation (rebound phenomenon) of topical steroids. However, seborrheic dermatitis is rather a sebostatic disease despite its name and occurs mostly on dry facial skin types. The pathogenesis of seborrheic dermatitis is unclear; however, *Pityrosporum ovale* (globosa species) and other microbes have been implicated. Treatment with 2% ketoconazole cream alone or in conjunction with hydrocortisone, 1–2.5% hydrocortisone cream, 1% hydrocortisone plus clioquinol, are all effective, but none provides permanent relief; treatment must be repeated periodically when this chronic condition flares [71].

Excoriated acne (*picker’s acne, acné excoriée des jeunes filles*) is seen primarily in girls with compulsive neurotic habit of picking the face and squeezing comedones, with subsequent secondary lesions and scarring. It may be a sign of depression [72]. Topical antiacne regimes may be helpful; however, covering cosmetics and psychosomatic therapy are the treatment of choice.

Hidradenitis suppurativa and dissecting cellulitis of the scalp may be associated with acne conglobata; an association known as follicular occlusion triad (or tetradre if associated with pilonidal sinus). This condition may also be associated with pyoderma gangrenosum and aseptic arthritis (PAPA syndrome) [73]. Systemic antibiotics and isotretinoin may help but surgical excision of the involved areas is still the treatment of choice.

Acne aestivalis also known as Mallorca acne is a rare dermatosis considered by some authors to be UV light-induced and by others as a variant of polymorphic light eruption. It is characterized by dome-shaped red small papules 3–4 mm that develop on the cheeks, commonly also on the sides of the neck, chest, shoulders and upper arms. Comedones and pustules are absent. The condition starts in the spring and progresses during the summer but resolves in the fall [74]. Supporting topical anti-inflammatory acne treatment may be applied.

### 6.1.10 Experimental Approaches

Current experimental data provided evidence for a modified scheme for acne etiology [16], thus indicating new therapeutic approaches. Androgens [77], proinflammatory skin lipids [78], inflammatory signaling also leading to comedogenesis, and regulatory neuropeptides have been implicated. Treatment will, likely, include new agents, such as new antiandrogens [41, 42], leukotriene inhibitors [79, 75], and ectopeptidase inhibitors [76], which may target one or more of these factors. The role of regulatory neuropeptides in the development of acne lesions brings a new insight into the association of stress and acne. Substance P immunoreactive nerve fibers were detected in close apposition to the sebaceous glands, and expression of the substance P-inactivating enzyme neutral endopeptidase was observed within sebaceous germative cells of acne patients [77]. In vitro experiments, using an organ culture system, demonstrated substance P-induced expression of neutral endopeptidase in sebaceous glands in a dose-dependent manner. On the other hand, treatment of sebocytes with IL-1β, which resulted in marked increase of IL-8 release [24], was partially blocked by co-incubation of the cells with α-melanocyte-stimulating hormone in a dose-dependent manner [78]. Corticotrophin-releasing hormone induces the synthesis of sebaceous lipids in vitro [79] and the synthesis of proinflammatory cytokines (IL-6, IL-8), which are also upregulated by leukotrienes [75], whereas adrenocorticotropic hormone evokes adrenal dehydroepiandrosterone to regulate skin inflammation [76]. These current findings indicate that central [77] or topical stress [79, 78] may, indeed, influence the feedback regulation, thus inducing the development of clinical inflammation in early acne lesions.

Phototherapies using blue light (peak at 414 nm) and mixed blue and red light (peaks at 415 and 660 nm) are being assessed as potential treatments for acne. First data indicate a reduction of lesions in mild to moderate acne after 4–12 weeks [79, 75], but the results are yet to be confirmed. Likewise, photodynamic therapy has been reported to be effective with virtually few side effects [76], however, current experimental data indicate a scarring effect of photodynamic treatment on the
sebaceous gland, a fact that defines sebaceous gland-rich areas being contraindicated for photodynamic treatment [77]. The usefulness of certain laser treatments in the management of acne scarring is also under evaluation. Hypertrophic and erythematous facial scars improved under treatment with the 585 nm flashlamp-pumped pulsed dye laser, and severe atrophic facial acne scars with the CO₂ laser [78, 79].

6.1.11 Global Variation

Acne is the most common skin disease with a worldwide distribution and affects all races with no known global variation. Some cosmetic agents and hair pomades may worsen acne. The practice is commonly registered in Africa and among Afroamericans.

Take Home Message

There is no cure for acne and it is not limited to the teenage years and, indeed, it may persist well into the fourth and fifth decades of life. With early and adequate treatment, the risk of permanent scarring can be dramatically reduced. Combination therapies work better. Patient’s education, cooperation and strict adherence to treatment instructions play an important role in the overall response and outcome. All acne treatments work relatively slow and appreciable improvement is generally seen after 1–2 months of beginning of therapy.

References

6.1 Acne and Its Variants


6.1 Acne and Its Variants


6.2 Rosacea and Related Diseases

Mohamed Badawy Abdel-Naser and Christos C. Zouboulis

6.2.1 Introduction

Rosacea is a chronic inflammatory condition of the central face that affects approximately 2% (south Europe) -10% (northern Europe) of different populations worldwide. The condition was thought to primarily affect fair skinned Caucasians, however, several studies have shown that all races including people with colored skin are affected [1, 2]. Although not a life-threatening disease, rosacea produces conspicuous facial redness and, in some patients, papules, pustules and rhinophyma that can have a deep impact on a patient’s quality of life. In particular, rhinophyma; the most prominent feature of advanced rosacea, is often mistakenly associated with alcoholism, as portrayed to the public as “drinker’s nose,” further stigmatizing rosacea patients. A survey by the National Rosacea Society reported that rosacea in up to 70% of patients has adversely affected their self-esteem and their social life [3]. Because rosacea is a condition that can now be easily diagnosed and effectively managed in most patients, much of this suffering is unnecessary [4].

6.2.2 Etiology and Pathophysiology

The etiology of rosacea is unknown [5]. Abnormal vascular reactivity, climatic exposures, matrix degeneration, chemicals and ingested agents, pilosebaceous unit abnormalities, and microorganisms such as Helicobacter pylori and Demodex folliculorum have been suggested to play a role in its development [6]. However, conclusive evidence incriminating any of these factors is lacking, and the cause of rosacea remains elusive. Furthermore, the distinct subtype of rosacea is likely determined by a
patient’s unique sensitivity to these triggers, as it is unlikely that flushing and rhinophyma have a common pathophysiologic factor [4].

Nevertheless, the pathologic process of rosacea is well described. The erythema of rosacea is caused by dilatation of the superficial vasculature of the face largely believed to be due to the atrophy of the supporting papillary dermis [7]. This has been confirmed by Laser-Doppler flowmetry studies that showed three to four times increase of lesional blood flow in rosacea patients when compared with control subjects [8]. Triggering factors such as sunlight; alcohol, spicy foods, certain drugs, acutely felt emotional stress, hot drinks, exercise, cold or hot weather, and hot baths and showers may worsen the condition by increasing cutaneous blood flow either directly such as sunlight and alcohol, or indirectly through autonomic nerve stimulation such as spicy foods. Inflammation also plays an important role, and inflammatory cells release proinflammatory mediators and degenerative enzymes that damage dermal constituents and clinically appear as erythema, papules, pustules and lupoid papules. Edema can develop as a result of increased blood flow and/or inflammation and may contribute to late fibroplasia and rhinophyma [9, 10].

### 6.2.3 Clinical Characteristics and Diagnosis

Rosacea develops insidiously, and several patients mistakenly assume that the facial lesions are adult acne, sun- or windburn-induced, or normal effects of aging. Correct diagnosis and early treatment of rosacea are important because, if left untreated, rosacea can progress to irreversible disfigurement and vision loss [11]. Rosacea is regarded as a vascular disorder generally involving the cheeks, chin, and forehead, and almost exclusively in men, also the nose [12]. There are four acknowledged general stages of rosacea [13]. In rare cases, extrafacial rosacea may occur.

Stage I, also termed as prerosacea, is characterized by frequent episodes of flushing often associated with burning and stinging sensation that may start as early as in childhood, though the typical age of onset is above 30 years [1]. Several drugs can cause the sudden or gradual appearance of a red, burning face. Any drug that releases histamine, vasoactive peptides (substance P), or prostaglandins can cause facial flushing. Examples of these types of drugs are nitroglycerin, nifedipine, monosodium glutamate, niacin, vancomycin, calcitonin, prostaglandin E, disulfiram (anatabase), and drugs containing ethanol. Flushing can also be seen in several other conditions such as menopause and perimenopause, pheochromocytoma, carcinoid tumor, and systemic mastocytosis [14].

Stage II rosacea is vascular and is manifested by persistent erythema of midface, commonly with slight telangiectasias (Fig. 6.2.1).

Stage III rosacea occurs in a minority of erythrotic patients (19%); here, the facial redness deepens and becomes permanent. Telangiectasias increase, and papules and pustules begin to develop, thus resembling acne vulgaris except that comedones are absent (Fig. 6.2.2). During this stage, ocular changes, such as conjunctivitis and blepharitis, and edema above nasolabial folds may develop [15].

Stage IV affects only a few patients, almost exclusively men. There is continued and increased skin and ocular inflammation. Ocular inflammation can progress to keratitis and result in the loss of vision. Erythrosis confined to the nose and fibroplasias and sebaceous hyperplasia result in nasal enlargement, i.e., rhinophyma [11, 12].

In addition, rosacea can affect body regions other than face and neck (extrafacial rosacea). Bald scalp, chest, back and limbs including palms that may show isolated pustules may be affected. Rosacea in peripheral locations may or may not be accompanied by facial manifestations [16].

The aforementioned classification system implies a gradual progression from prerosacea to advanced disease; a clinical course that is uncommonly seen. In 2002, an expert committee assembled by the National Rosacea Society explicitly defined and classified rosacea into four different subtypes and a variant based on specific clinical signs and symptoms [17]. These subtypes are:

- Erythematotelangiectatic (subtype 1) that closely resembles stage II
- Papulopustular rosacea that resembles stage III (subtype 2)
- Phymatous rosacea that resembles stage IV (subtype 3)
- Ocular rosacea (subtype 4)
- Granulomatous rosacea as a variant form

Stage I, i.e., prerosacea, was not included as a separate subtype as it is nonspecific being also caused by several other conditions, and ocular rosacea was assigned a separate subtype as skin symptoms and signs of rosacea.
are not a prerequisite to the diagnosis [18]. Patients may have the characteristics of more than one subtype at the same time [17]. As prerosacea is a stage that can also be medically controlled, it is plausible to extend the classification of the National Rosacea Society and include this entity as subtype 0 (Table 6.2.1).

The exact pathophysiology of rosacea is unknown and currently, the therapeutics of rosacea empirically target the signs and symptoms. Therefore, the classification system of the National Rosacea Society Committee aids clinicians in treatment by highlighting the preponderance of one or more of the clustering signs of presentation and, thus, helps specify which therapeutic approach to initiate.

### 6.2.3.1 Erythematotelangiectatic Subtype

Central facial flushing, often accompanied by burning or stinging, is the predominant sign in erythematotelangiectatic rosacea. The redness usually spares the periocular skin. These patients usually have a fine
textured skin that lacks sebaceous quality, which is a characteristic feature of other subtypes. The erythematous areas of the face at times appear rough with scales likely due to chronic, low-grade dermatitis. Frequent triggers to flushing include acutely felt emotional stress, hot drinks, alcohol, spicy foods, exercise, cold or hot weather, and hot baths and showers. These patients also report that the burning or stinging is exacerbated when topical agents are applied.

6.2.3.2 Papulopustular Rosacea Subtype

Papulopustular rosacea is the classic presentation of rosacea. Patients are middle aged individuals, who predominately present with a red central portion of their face that contains small erythematous papules surmounted by pinpoint pustules. One may elicit a history of flushing. Telangiectasias are likely present but may be difficult to distinguish from the erythematous background in which they exist.

6.2.3.3 Phymatous Rosacea Subtype

Phymatous rosacea is defined as marked skin thickenings and irregular surface nodularities of the nose, chin, forehead, one or both ears, and/or the eyelids. Four distinct histologic variants can occur with rhinophyma (associated changes of the nose) that include glandular, fibrous, fibroangiomatous, and actinic characteristics.

6.2.3.4 Ocular Rosacea Subtype

Ocular manifestations may precede the cutaneous signs by years. Yet, frequently, they develop concurrently with dermatologic manifestations. The ocular manifestations include blepharitis, conjunctivitis, inflammation of the lids and meibomian glands, interpalpebral conjunctival hyperemia, and conjunctival telangiectasias. Patients may report eye stinging or burning, dryness, irritation with light, or foreign body sensation.

6.2.3.5 Granulomatous Rosacea Variant

This condition is characterized by distinct clinical presentation in the form of discrete slightly erythematous or flesh colored firm papules or nodules in the face with involvement of the eyelids and upper lip which are areas not affected by rosacea. In addition, it lacks the erythema and telangiectasias (Fig. 6.2.3). The condition may be severe and heal with scarring; occasionally it may also be generalized and appear on the extremities or trunk. Old terminologies for this variant are lupoid rosacea, lupus miliaris disseminatous faciei, and rosacea-like tuberculid Lewandowsky.

The diagnosis of rosacea is clinical, and skin biopsy may be supportive. Several skin conditions share some clinical features with rosacea. Allergic contact dermatitis, phototoxic dermatitis, atopic dermatitis, erysipelas, malar rash of lupus erythematosus, dermatomyositis, mixed connective tissue disease, angioedema, scleredema adulturnorum of Buschke, and Haber’s syndrome (rare variant of the Dowling-Degos disease with rosacea-like erythema of the face) cause mild erythema similar to erythematotelangiectatic rosacea. Besides
379

6.2 Rosacea and Related Diseases

acne vulgaris, seborrheic dermatitis, perioral dermatitis, pustular folliculitis and steroid induced acne are similar to papulopustular rosacea. However, these conditions lack the characteristic flushing, telangiectasias, papules, and pustules of rosacea. Sarcoidosis (lupus pernio) can closely mimic phymatous and granulomatous rosacea by producing red papules on the face, but the disease will usually manifest itself in other organs as well. Other conditions include leonine facies of lepromatous leprosy or leukemia, familial nevoid hyperplasia, Melkersson Rosenthal syndrome and acromegaly [19].

6.2.4 General Therapeutic Outlines

Rosacea should be treated at its earliest manifestations to mitigate progression to the stages of edema and irreversible fibrosis. The outcome of the unknown etiology and the poor understanding of the pathophysiology of rosacea is that treatment is directed at disease endpoints rather than targeting the underlying pathogenic mechanisms, i.e., symptomatic control rather than cure. Accordingly, flushing is treated with vasoconstrictors, telangiectasias with vascular lasers,
inflammation with anti-inflammatory agents and papules and pustules with anti-inflammatory antibiotics.

Rosacea usually responds satisfactorily to treatment, but improvement is gradual and requires patience, as well as perseverance. Patient education is the milestone in the management of this condition. Before the initiation of therapy, the triggering factors that exacerbate the disease should be identified and avoided if possible. These factors may be unique to each individual patient, and every effort must be exerted to convince the patients to follow these simple but effective general guidelines [20].

- Rosacea patients should wash their face with lukewarm water using a gentle liquid cleanser. A soft towel is recommended for drying the face. Special rosacea cleansers, e.g., those containing sodium sulfacetamide and sulfur may be used.
- Cosmetic products containing alcohol, menthol, eucalyptus oil, and fragrances and greasy products requiring solvents to be removed or containing sodium lauryl sulfate are better avoided to minimize irritation of the skin.
- Electric shavers rather than blades are recommended for male patients. Sharp blades should be used if electric shavers are not available.
- Massaging the nose, cheeks and forehead each evening using a lubricant or during application of a topical therapy may be of benefit in the presence of facial edema through acceleration of lymphatic drainage.
- There is no rosacea-specific diet but avoidance of alcohol, hot beverages containing caffeine, and spiced food is recommended as they cause facial vasodilatation with subsequent aggravation of symptoms.
- Flushing in a hot environment can be prevented for up to 30 min by holding ice ships in the mouth.
- Cosmetic coverage of facial redness and telangiectasia leads to an improved appearance. Care must be taken to use only those that are nonirritating, hypoallergenic, and noncomedogenic. There are several cosmetic products available for rosacea, all of which are characterized by a green tint.
- Sunscreen: The daily use of broad-spectrum sunscreen is recommended for all patients with rosacea irrespective of the subtype. A sunscreen that protects against both ultraviolet A and ultraviolet B light should be chosen. Physical blockers such as titanium dioxide and zinc oxide are well tolerated by rosacea patients who are known to have a sensitive skin. Also, the sunscreen should contain protective silicones, such as dimethicone or cyclomethicone. Green tinted sunscreens can cover the erythema. Sodium sulfacetamide and sulfur containing sunscreens are available and provide a dual therapeutic effect [21].

Facial rosacea skin is extremely sensitive to topical therapeutic agents that are rarely tolerated. Nevertheless patients are instructed to continue treatment as this sensitivity decreases with the improvement of their
affected skin. In addition, patients have commonly been on topical steroids that may have induced perioral dermatitis and steroid induced rosacea. Sudden withdrawal of topical steroids is therefore expected to initially worsen patients’ condition due to rebound phenomenon and proper explanation of this fact will encourage patients to abandon use of topical steroids [9]. In the authors’ experience, gradual withdrawal of topical steroids coupled with gradual introduction of nonsteroidal topical therapeutics is convenient and tolerable and is associated with low discontinuation rate. This procedure is likely to decrease the effect of the expected rebound phenomenon and that of the initial irritation of the nonsteroidal topical therapies and therefore would be acceptable mostly to female patients, who are extremely concerned about their facial condition.

6.2.5 Currently Established Therapies

Prerosacea (subtype 0 or stage I) patients, who face problems of frequent flushing, may benefit from vasoconstrictor drugs currently in use for migraine. Clonidine tablets at dosage of 0.05-0.075 mg twice daily has proved to be effective by lowering baseline malar temperature without reduction of blood pressure [22]. Other drugs that can be tried include β-blockers in low doses (nadolol 20 mg once or twice daily), aspirin, naloxon and ondansetron. Flushing occurring at any other stage or subtype can similarly be treated. In general, the severity of flushing is rarely of a sufficient magnitude to make medical therapy necessary [4].

Erythematotelangiectatic rosacea (subtype 1 or stage II) is the most difficult subtype to treat. There is little evidence that topical agents or oral antibiotics are effective in the treatment of erythema, telangiectasia and flushing. Low dose isotretinoin (10 mg once or twice daily) given for 4 months may improve erythema but teratogenicity, as a major side effect, is a limiting factor [23].

The most effective modality is vascular lasers and intense pulsed light (IPL) devices. Vascular lasers include pulsed dye laser (585 or 595 nm), the potassium-titanyl-phosphate laser (532 nm), and the diode-pumped frequency-doubled laser (532 nm). These wavelengths allow selective absorption by oxyhemoglobin, leading to vessel reduction with minimal damage to the surrounding tissue or scarring. To be effective against deeper facial vessels longer wavelengths of lasers are required, including the diode laser (810 nm), the long-pulsed Alexandrite laser (755 nm), and the long-pulsed Nd:YAG laser (1,064 nm). Multiple sessions may be necessary and pulse stacking or repeat passes may increase efficacy without adverse effects [24, 25].

IPL is a noncoherent polychromatic light of a broadspectrum of wavelengths (515–1,200 nm), which can be altered by cut-off filters to adjust to the patient’s skin type and lesion depth. The nonfixed wavelengths offer the advantage of treating telangiectasia at different dermal depths since longer wavelengths penetrate more deeply and the large spot size with IPL make it simpler to treat an entire face. It is also useful for facial rejuvenation, affecting not only vascular lesions, but also pigmented lesions (photodamage), which are common in old age [26]. A significant decrease in blood flow, telangiectasia, and intensity of erythema was succeeded following five treatment sessions at 3-week intervals using 515 nm filter and a pulse duration of 3 ms [27]. Permanent telangiectasia may be treated by electro surgery if facilities for laser or IPL are unavailable. However, facial erythema is not improved, and new telangiectasias develop with the passage of time.

Papulopustular rosacea (subtype II or stage 3) is the easiest subtype to treat. Most patients respond favorably to topical metronidazol, sodium sulfacetamide-sulfur and azelaic acid, which are FDA approved for treatment of rosacea and are considered as first line agents. Topical metronidazol, an imidazole antibiotic, is available in a variety of strengths and vehicle formulations, including 0.75% gel, lotion and cream as well as 1% cream and gel. It has been suggested that its efficacy is related to its anti-oxidant and anti-inflammatory properties. Topical skin reactions are rare occurring in less than 2% of patients [28]. Sulphacetamide 10% and sulfur 5% combination therapy was originally used to treat acne and seborrheic dermatitis. The problem of its unpleasant odor has been concealed and it is also available as a cream, lotion, gel, topical suspension, cleanser and a silica-based mask [4]. The cleanser form can be used in combination with topical metronidazole to provide an additive effect. The keratolytic effect of sulfur and the antibacterial effect of sulfacetamide are suggested to be the main mechanisms of action [29]. Azelaic acid, a naturally occurring dicarboxylic acid, is another antirosacea agent available in 15% gel and 20% cream
formulations. Its mechanism of action is similar to metronidazole, i.e., due to anti-oxidant and anti-inflammatory effects [30]. The favorable tolerability profile, the high compliance and low discontinuation rate caused by topical skin reactions are the main advantages of the topical azelaic acid use [31].

Several other topical preparations can be used as alternative therapies. Benzoyl peroxide 5% and clindamycin 1% combination once daily was effective in decreasing inflammatory lesions and erythema [32]. Topical retinoids, including tretinoin, tazarotene, and adapalene reduce inflammatory lesions in rosacea; however, their use is limited by the induction of significant irritation to the sensitive facial skin [21]. Topical calcineurin inhibitors such as pimecrolimus and tacrolimus significantly improved inflammatory lesions of rosacea in an open prospective study [33]. Interestingly, rosaceiform eruption was an adverse effect of their use on the face and more data are needed before a final conclusion can be made [34]. Permethrin in a 5% cream was equally effective as 0.75% metronidazole gel and its efficacy has been attributed to eradication of Demodex folliculorum [35]. Nonfluorinated short-term topical steroid lotions can be used in severe inflammatory rosacea [36]. According to the authors' experience, short-term topical steroids dramatically reduce most of rosacea symptoms and therefore are greatly appraised by patients. Steroids are given for a week and gradually tapered and concomitantly replaced by nonsteroidal preparation over a subsequent period of 1 or 2 weeks.

Patients with severe inflammatory rosacea, whose immediate response is paramount, will benefit from combined oral and topical therapy. The combination therapy reduces initial prominent symptoms, prevents relapse when oral therapy is discontinued, and maintains long-term control. Oral therapy is generally continued until inflammatory lesions clear or for 12 weeks, whichever comes first [37]. Tetracyclines, such as tetracycline (250–1,000 mg daily), doxycycline (50–200 mg daily) and minocycline (50–100 mg daily), and erythromycin (250–1,000 mg daily) are the first line therapy. Doxycycline hyclate 20 mg twice daily has also been reported to be effective in treatment of rosacea with a low incidence of adverse effects including emergence of bacterial strains. The drug acts by inhibiting the metalloproteinases-2 and -9 that break down capillary vessel basement membrane and down-regulates cytokines that contribute to inflammation and erythema. Erythromycin is used in patients intolerant to tetracyclines and during pregnancy.

As an alternative, second generation macrolides, such as clarithromycin (250 mg twice daily) and azithromycin (500 mg daily) have shown to work faster and with lesser side effects, such as gastrointestinal tract manifestations, than tetracyclines and erythromycin. The high cost of the second-generation macrolides is the main limiting factor [4, 38].

Oral metronidazole at a dosage of 200 mg, twice daily, is equally effective as tetracyclines and can be also used during pregnancy [4, 39]. Recalcitrant cases of rosacea may be successfully treated with 0.5 mg/kg/day isotretinoin and even with a lower dose (10 mg once or twice daily). Isotretinoin does not result in antibiotic resistance but has serious side effects, most notably its teratogenic potential. Female patients of childbearing age must be strongly advised to use effective birth control [23]. Dapsone may also be used in refractory cases where isotretinoin is contraindicated [40].

### 6.2.5.1 Phymatous Rosacea (Subtype III, Stage 4)

The mainstays of treatment are isotretinoin and surgical correction. This varies from other rosacea subtypes. Isotretinoin may halt the progression of rhinophyma and reduce its volume, but does not induce total resolution [41]. Surgical treatment including cryosurgery, electrotherapy and dermabrasion or laser ablation is necessary to eradicate excess hyperplastic tissue [4]. There is little evidence that phymatous growths will benefit from any topical treatment.

### 6.2.5.2 Ocular Rosacea (Subtype IV)

Ocular rosacea, similar to phymatous rosacea, has a distinct therapeutic management. Therefore, dermatologists must ask their patients specifically about ocular symptoms and perform a thorough physical examination to rule out this type of rosacea. Mild eye affection responds well to topical agents (artificial tears during the day and antibiotic ointment at night) and eyelid hygiene. Markedly affected eyes respond promptly to virtually any oral antibiotic; tetracyclines are preferred
due to their relative safety [42]. Isotretinoin can be used in severe forms not responding to other measures. Advanced cases may benefit from surgical interference, e.g., keratoplasty as required [18].

6.2.5.3 Granulomatous Variant

Treatment of this rosacea variant is similar to that of papulopustular rosacea. Severe cases also show a dramatic favorable response to oral and intralesional corticosteroids [4].

6.2.5.4 Rosacea Conglobata

Similar to acne rosacea, lesions may rarely develop into painful hemorrhagic purulent pustules and nodules with confluence leading to fistules with a chronic progreident course [43]. Like in all rosacea variants comedones are missing. The lesions respond well to short-term oral corticosteroids (30 mg daily) in combination with isotretinoin.

6.2.6 Rosacea-Related Disorders

The National Rosacea Society expert committee noted that certain disorders may have been prematurely identified as being associated with rosacea or as a variant of rosacea, and for clarity, they should be recognized at this time as separate entities. There is insufficient basis at present to include the following conditions as types of rosacea [17].

6.2.6.1 Rosacea Fulminans

Popularly known as pyoderma faciale, the grouping of rosacea fulminans as a type of rosacea is premature. It is characterized by the sudden appearance of papules, pustules, and nodules, along with fluctuating and draining sinuses that may be interconnecting. Fistulae formation can also occur. In contrast to acne fulminans, no general symptoms such as fever, weakness and joint pains are present. The condition appears primarily in women in their 20s, and intense redness and edema may also be prominent. Systemic short-term steroids are effective in controlling this condition [44].

6.2.6.2 Steroid-Induced Acneiform Eruption

Steroid-induced acneiform eruption is not a variant of rosacea and can occur as an inflammatory response in any patient during or after chronic corticosteroid use. The same inflammatory response may also occur in patients with rosacea. However, commonly several rosacea patients and others continue therapy against instructions of dermatologists with ultimate steroid side effects and worsening of rosacea symptoms. Dermatologists commonly encounter not only rosacea patients but also patients with facial dermatoses who have already been on treatment with steroids usually potent with erythrotic rosacea. In these cases the border between genuine rosacea and steroid rosacea is not easy to establish [44]. Gradual withdrawal of the topical steroid with concomitant introduction of antirosacea treatment is associated with low discontinuation rate. Some experts prefer gradual withdrawal with use of topical emollients to be followed by rosacea treatment and when the symptoms of the rebound phenomenon disappear. Topical calcineurin inhibitors (pimecrolimus, tacrolimus) offer an alternative to classical antirosacea treatments in order to effectively withdraw corticosteroids [43].

6.2.6.3 Perioral Dermatitis

Although rosacea papules may appear in the perioral area, perioral dermatitis without rosacea symptoms cannot be classified as a variant of rosacea. Perioral dermatitis is characterized by such stigmata as microvesicles, scaling, and peeling and the perioral topicalization. It also occurs at a younger age than rosacea [46].

6.2.6.4 Persistent Edema in Rosacea (Morbihan’s Disease)

Permanent facial edema in patients with rosacea develops through a major involvement of the lymphatic
vessels in addition to the blood vessels [47]. The forehead, the nose, and the cheeks are primarily involved. The histological characteristic is the accumulation of mast cells in all dermal levels [49]. The currently discussed immune dysregulation (a form of contact urticaria) has still to be confirmed [47]. The treatment of this rosacea related disorder is similar to the other forms discussed above.

6.2.7 Complications to Avoid

Reduction of blood pressure by clonidine is a possible complication but it is rarely anticipated with the small dose used [4].

Purpuric eruptions were commonly seen; however, with the new nonpurpuric pulsed dye lasers, this problem has been obviated though multiple treatment sessions may be necessary to achieve a noticeable improvement. Patients should be informed that lasers and IPL do not offer cure and a maintenance program for generalized facial erythema could involve a laser or light treatment every 4–6 months [53].

Topical agents for rosacea are usually not tolerated by the sensitive facial skin. Gradual stepwise application will diminish the intolerability and will encourage the patient to continue the treatment. Frequently patients have been on topical corticosteroids for a long time and patients should be expecting an initial worsening of the disease on corticosteroid withdrawal [10].

Several complications may arise with the use of systemic therapy. Gastrointestinal distress, candida-induced vulvovaginitis and rarely pseudotumor cerebri may occur with tetracycline use. Avoidance of sun exposure protects against the photosensitivity of doxycycline. Minocycline may result in vertigo and blue dyspigmentation. These complications require shifting to erythromycin which is almost without complications [4]. Gastrointestinal disturbances that resolve spontaneously, erythematous skin rash, and peripheral neuritis rarely occur with oral metronidazole use. Alcohol abstinence is also required to avoid a disulfiram-like reaction and headache [39]. Antibiotic resistance from prolonged antibiotic use may occur and isotretinoin is an alternative. Retinoids result in excessive dryness that can be overcome by nongreasy emollients for skin and artificial tears for the eyes [42].

6.2.8 Experimental Approaches

Topical vitamin C (5.0% L-ascorbic acid cream) daily could improve erythema in 75% of the cases [50]. It was suggested that free-radical production may play a role in the inflammatory reaction of rosacea, and that the antioxidant effect of L-ascorbic acid may be responsible for its effect. These promising preliminary results still need to be confirmed in larger, long-term studies.

Similarly, over the counter medications containing herbs are commonly used by patients who are often dissatisfied with traditional medical treatment. Commonly used plants include licorice, feverfew, green tea, oatmeal, lavender, chamomile, tea tree oil and camphor oil. Few of these ingredients have been evaluated in clinical trials but the efficacy has not been established; nevertheless dermatologists should be aware of what patients are using and be able to direct them further [51].

Photodynamic therapy with IPL preceded by application of topical aminolevulinic acid for 15–60 min has been approved for treatment of actinic keratoses and is being evaluated in rosacea. Photodynamic therapy is suggested to be of particular value in rosacea patients with concomitant photodamage [52]. Similarly a combination of laser and light source therapy is currently evaluated for optimizing results in patients with both telangiectasia and flushing [48].

6.2.9 Global Variation

Despite earlier beliefs that rosacea is primarily a disease of light-skinned Caucasians, recent studies have shown that all races including people with dark skin are affected. [1, 2]. Erythema may be more difficult to recognise in patients with skin types IV and V, but papules, pustules and granulomatous lesions are commonly seen. In most countries women patients predominate especially in the early stages as they are concerned about their faces and seek cosmetic advice more often than men [1].
Take Home Messages

- Rosacea is an enigmatic disease with multiple exacerbations and remissions, and treatment is directed toward symptomatic control rather than cure. Medical therapy is chosen based on the severity of presentation. When possible, a stepwise approach can be undertaken, applying measures to diminish facial skin sensitivity followed by topical and oral anti-inflammatory medications including antibiotics, with late surgical intervention as required.
- As can be implied by the number and variety of treatment options available for rosacea, no single therapeutic regimen has been found effective in all cases, and many cases of rosacea are recalcitrant to multiple therapies. Therefore, treatment must always be tailored to each individual, and various options must be explored until symptoms begin to respond favorably. A treatment plan that combines pharmacotherapy with appropriate skin care and trigger avoidance will achieve the best overall results.

References

Part VII

Autoimmune Diseases
7.1 Etiology and Pathophysiology

7.1.1 Pemphigus Group

The basic pathophysiology of pemphigus is that the circulating IgG autoantibodies inhibit the adhesive function of desmogleins (Dsg1 and Dsg3) and cause the loss of keratinocyte cell-to-cell adhesion (acantholysis in histology), with resultant blister formation. Dsg1 and Dsg3 are cadherin-type cell-to-cell adhesion molecules that are expressed in the skin and mucous membranes where blisters and erosions are found in patients. IgG autoantibodies in pemphigus are detected...
in essentially all patients with active disease, as determined by direct immunofluorescence for in vivo-bound antibodies and by indirect immunofluorescence or enzyme-linked immunosorbent assay (ELISA) for circulating antibodies [1, 2]. The titers of circulating IgG autoantibodies are usually correlated with disease activity [3, 4].

IgG autoantibodies against Dsg1 and Dsg3 are pathogenic and play a primary role in inducing blister formation in pemphigus [5, 6]. Essentially, all patients with pemphigus have IgG autoantibodies against Dsg1 and/or Dsg3, depending on the subtype of pemphigus [1, 3]. When antidesmoglein IgG autoantibodies are removed from the patient’s sera in pemphigus vulgaris, pemphigus foliaceus, or paraneoplastic pemphigus (PNP) by immunoadsorption with recombinant desmoglein proteins, the sera are no longer pathogenic in the blister formation [7, 8]. Furthermore, antidesmoglein IgG autoantibodies affinity-purified from pemphigus sera on the desmoglein recombinant proteins can cause blisters when injected into neonatal mice [8, 9]. IgG autoantibodies against acetylcholine receptors or annexin-like molecules have been reported, but their pathogenic relevance in pemphigus remains to be determined [10–12].

The gross, as well as histological, sites of blisters in pemphigus vulgaris and foliaceus are logically explained by desmoglein compensation theory [13, 14]. For example, when sera contain only anti-Dsg1 IgG, which interferes with the function of Dsg1, the presence of Dsg3 compensates for the loss of function of Dsg1 in the lower epidermis. In contrast, in the upper epidermis, there is no compensation by Dsg3; therefore, blisters only appear in the superficial epidermis of the skin. Although the anti-Dsg1 IgG binds to the mucosa, no blisters are formed because of the co-expression of Dsg 3. Thus, sera containing only anti-Dsg1 IgG causes superficial blisters in the skin without mucosal involvement, as observed in patients with pemphigus foliaceus.

Patients with PNP develop characteristic IgG autoantibodies against the multiple plakin molecules that are thought to play a role in anchoring keratin filaments to cell membranes, e.g., desmoplakin I, II, BP230, envoplakin, periplakin, and plectin, in addition to IgG autoantibodies against Dsg3 and/or Dsg1 [15]. It is also important to bear in mind that not only humoral immunity, but also cell-mediated cytotoxicity, is involved in the pathogenesis of PNP, in which more severe and refractory oral erosions and stomatitis, as well as more polymorphic skin eruptions, are observed compared with classic forms of pemphigus.

7.1.1.2 Bullous Pemphigoid

Bullous pemphigoid (BP) is an autoimmune inflammatory skin disease characterized by in vivo deposition of IgG autoantibodies and complement components in the basement membrane zone [16]. On direct immunofluorescence, biopsies of perilesional skin show linear deposits of C3 along the dermal–epidermal junction in most cases. Linear IgG deposition is also present in most cases. Indirect immunofluorescence indicates circulating antibasement membrane autoantibodies of IgG and, less frequently, IgA and IgE in approximately 70–80% of patients [17, 18].

Patients with BP have circulating IgG autoantibodies against two hemidesmosomal components: BP230 (BPAG1 or BP230) and BP180 (BPAG2 or type XVII collagen). BP230 is a cytoplasmic protein found in the plaque of hemidesmosomes and is a member of the plakin family, which plays a role in anchoring keratin intermediate filaments to hemidesmosomes. BPAG2 is a transmembrane protein with intermittent collagenous extracellular domains that are localized to anchoring filaments. Most patients have IgG autoantibodies that recognize a particular epitope in a small noncollagenous region that is located just outside the membrane, called the NC16a domain [19]. The initial step of blister formation is considered to be the binding of antibody to BP180, followed by the activation of complement components, chemotaxis of leukocytes, degranulation of mast cells, and recruitment of inflammatory cells (neutrophils, and eosinophils). These cells produce various chemokines and proteases such as gelatinase, neutrophil elastase, and matrix metalloproteinase-9 (MMP-9), which degrade BPAG2 and result in epidermal–dermal separation [20–22].

Epidermolysis bullosa acquisita is a rare autoimmune bullous disease. Patients with epidermolysis bullosa acquisita have circulating and tissue-bound IgG autoantibodies against type VII collagen, which is a major component of anchoring filaments. Circulating IgG antibodies can be detected in approximately 50%
of patients with the disease by indirect immunofluorescence. It is useful to use 1 M salt-split skin as a substrate to differentiate between epidermolysis bullosa acquisita and BP; the former stains the dermal side whereas the latter stains the epidermal side [23]. The antibodies are directed against multiple epitopes on the N-terminal noncollagenous domain of type VII collagen. Electron microscopy demonstrates IgG deposition on the lower part of the lamina densa of the basement membrane zone. The exact mechanism of blister formation is still unknown. Many studies suggest that the autoantibodies, together with the complement system, mediate leukocyte infiltration and dermal–epidermal separation [24]. Recently, murine models were developed that can histologically and immunopathologically mimic epidermolysis bullosa acquisita [25, 26].

7.1.2 Clinical Characteristics and Diagnosis

7.1.2.1 Clinical Characteristics

7.1.2.1.1 Pemphigus Vulgaris

Pemphigus vulgaris has two clinical subtypes: mucosal-dominant type and mucocutaneous type. Patients with mucosal-dominant type show mucosal erosions mainly in the oral cavity, with minimal or limited skin involvement. Patients with mucocutaneous type show extensive flaccid blisters and erosions on the skin in addition to mucosal erosions. Any stratified squamous epithelia in which Dsg1 and/or Dsg3 are expressed can be involved in pemphigus vulgaris.

Essentially all patients with pemphigus vulgaris develop mucous membrane lesions that are usually observed as painful erosions. Scattered and often extensive erosions may be observed on any part of the oral cavity. Extensive erosions and painful lesions in the mouth may result in decreased food and drink intake. Involvement of the throat may produce hoarseness and difficulty in swallowing. The esophagus, conjunctiva, nasal mucosa, vagina, penis, anus, or labia may also be involved.

The primary skin lesion of pemphigus vulgaris is flaccid, thin-walled, easily ruptured blisters that appear anywhere on the skin surface (Fig. 7.1.1). The blisters are fragile and soon rupture to form painful erosions that ooze and bleed easily. The erosions rapidly become partially covered with crusts. Without appropriate treatment, pemphigus vulgaris can be fatal because large areas of the skin lose their epidermal barrier function, leading to the loss of body fluids or secondary bacterial infection. Because of the absence of cohesion in the epidermis, the upper layers are easily made to slip laterally by slight pressure or rubbing in active patients with pemphigus (Nikolsky’s sign).

7.1.2.1.2 Pemphigus Foliaceus

Patients with pemphigus foliaceus present multiple crusted erosions, often on an erythematous base, mainly in a seborrheic distribution, including the face, scalp, and upper trunk (Fig. 7.1.2). The primary lesion of small blisters is fragile and easily ruptured, leaving shallow erosions with some scales. Some patients with only a few scattered crusted lesions may be misdiagnosed as having impetigo. In severe cases, the lesions can involve the entire skin surface and present as exfoliative erythroderma. Mucous membranes are essentially not involved, even in widespread cases. The absence of oral involvement may be a clue to clinically differentiate pemphigus foliaceus from pemphigus vulgaris.
Paraneoplastic pemphigus (PNP) occurs in association with neoplasms such as non-Hodgkin’s lymphoma, chronic lymphocytic leukemia, Castleman’s tumor, malignant and benign thymoma, spindle cell neoplasms (reticulum cell sarcoma), and Waldenström’s macroglobulinemia. The most constant clinical feature of PNP is the presence of intractable stomatitis. Severe stomatitis is usually the earliest presenting sign and, after treatment, it is the one that persists and is extremely resistant to therapy (Fig. 7.1.3). This stomatitis consists of erosions and ulcerations that affect all surfaces of the oropharynx and characteristically extend onto the vermilion of the lip. Most patients also have severe pseudomembranous conjunctivitis with scarring.

The cutaneous lesions are quite polymorphic and may appear as erythematous macules, flaccid blisters and erosions resembling pemphigus vulgaris, tense blisters resembling BP, erythema multiforme-like lesions, and lichenoid eruptions. PNP is the only form of pemphigus that has involvement of the non-stratified squamous epithelia. Approximately 30–40% of patients develop pulmonary symptoms [27, 28]. The earliest symptoms are progressive dyspnea; pulmonary function studies show airflow obstruction involving large and small airways, as observed in bronchiolitis obliterans, which can be fatal through respiratory failure.

**7.1.2.1.3 Paraneoplastic Pemphigus**

Paraneoplastic pemphigus (PNP) occurs in association with neoplasms such as non-Hodgkin’s lymphoma, chronic lymphocytic leukemia, Castleman’s tumor, malignant and benign thymoma, spindle cell neoplasms...
7.1 Acquired Bullous Disease

7.1.2.1.4 Bullous Pemphigoid

The age of onset of the disease averages 65–75 years. The lesions usually consist of tense blisters on inflamed or normal-appearing skin (Fig. 7.1.4). In addition to the typical bullae, it often presents broad clinical features such as pruritus, urticarial eruptions, or erythematous plaques without blisters; these may lead to misdiagnosis, especially in the early stage of the disease. The mucosal membranes of the oral cavity, pharynx, urethra, and conjunctiva may be involved, but are less frequently affected than in pemphigus vulgaris. Several clinical variants of the disease exist: vesicular pemphigoid is characterized by small vesicles rather than bullae; dyshydrosiform pemphigoid is usually limited to the palms and soles; nodular pemphigoid presents skin lesions resembling prurigo nodularis; pretibial localized pemphigoid affects mainly older women and remains limited to the lower legs. The association of BP with malignancy has been discussed but is still controversial. Some case–control studies have failed to show a statistically increased incidence of malignancy in patients with BP [29].

7.1.2.1.5 Epidermolysis Bullosa Acquisita

Epidermolysis bullosa acquisita can affect both children and adults and has two clinical subtypes. One subtype is a noninflammatory mechanobullous type that mimics mild, dominant dystrophic epidermolysis bullosa. The other subtype is an inflammatory type that clinically resembles BP or cicatrical pemphigoid. Both types present skin fragility and trauma-induced blistering with erosions and usually heal with atrophic scarring and milia formation on the affected skin. Epidermolysis bullosa acquisita is also well known as a bullous disease present with other diseases such as bullous systemic lupus erythematosus (SLE), inflammatory bowel disease, amyloidosis, multiple myeloma, thyroiditis, diabetes mellitus, and multiple endocrinopathy syndrome. Mucous membrane involvement is variable.

7.1.2.2 Diagnosis

Once the diagnosis of pemphigus is suspected from clinical findings, it is important to take a biopsy for histology and direct immunofluorescence, as well as to perform serological tests to look for IgG autoantibodies against cell surfaces of keratinocytes or desmogleins. The definitive diagnosis of pemphigus requires the demonstration of IgG autoantibodies. Methods to demonstrate pemphigus autoantibodies include direct immunofluorescence, indirect immunofluorescence, and ELISA.

Direct immunofluorescence examines the patient’s skin or mucous membranes to demonstrate in vivo-bound IgG deposition on the keratinocyte cell surfaces and is the most reliable and sensitive diagnostic test for all forms of pemphigus (Fig. 7.1.5). If direct immunofluorescence is negative, diagnosis of pemphigus should be seriously questioned. IgM deposition is not observed, but occasionally IgA and complement (C3) deposition may also be observed.

ELISA provides a specific, sensitive, and quantitative assay to detect and measure circulating IgG autoantibodies in the diagnosis of pemphigus [1, 3]. The patient’s serum is tested on ELISA plates pre-coated with recombinant proteins of Dsg1 or Dsg3. ELISA allows the serological differentiation of subtypes of pemphigus vulgaris and foliaceus. Furthermore, ELISA scores show parallel fluctuations with disease activity. Thus, ELISA is also useful to monitor disease activity to plan tapering schedules of corticosteroids and to predict flares or relapses before clinical evidence is noticed.

Basically, the diagnosis of the pemphigoid group requires an approach similar to that of the pemphigus group. Direct immunofluorescence demonstrates in vivo-bound IgG and C3 in the basement membrane.
Once clinical remission is obtained, changes in the titers of circulating autoantibodies as determined by ELISA are helpful in gauging the dose of prednisone [1, 30–32]. Corticosteroids are also used in combination with other steroid-sparing agents such as azathioprine, mycophenolate mofetil, and cyclophosphamide. Other adjuvant therapies to achieve relatively rapid response include plasmapheresis and high-dose IVIG. The timing of the start of adjuvant therapies in combination with corticosteroids is still debatable. Currently available therapies for pemphigus are listed in Table 7.1.1.

In general, the quality of published data concerning therapy for autoimmune bullous diseases is poor. There are few controlled trials, partly because of the rarity of the diseases. The majority of data are confined to case reports and small case series with short follow-up periods and variable disease severity. Therefore, it is difficult to evaluate the efficacy of each treatment protocol and provide firm guidelines for treatment.

7.1.4 Current Established Therapies

7.1.4.1 Systemic Treatment

Systemic corticosteroids are the gold standard and are considered the first choice of treatment for all autoimmune bullous diseases.

*Prednisone:* Prednisone at 1.0 mg/kg/day (usually 60 mg/day) is a standard initial treatment for pemphigus. Clinical improvement can be observed within days of starting prednisone. The dosing schedules are largely empirical and based on practical experience. If there is no or a poor response in 5–7 days, the dose should be increased in 50–100% increments until disease control is achieved. If doses above 100 mg/day are required, pulse intravenous corticosteroids could be considered. The disease activity can be evaluated by the number of new bullae formed and the rate of healing of new lesions per day. Usually, once remission is obtained and maintained with healing of the majority of lesions, the dose of prednisone can be cautiously tapered. In the initial stage of treatment (mostly in the first 2–3 weeks), it is important to aim for rapid and complete remission with a sufficiently potent regime. If disease activity is still uncontrolled, adjuvant therapies should be considered.
Table 7.1.1 Therapeutic ladder for autoimmune blistering disease

<table>
<thead>
<tr>
<th>Standard treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic oral corticosteroids (usually prednisone)</td>
</tr>
<tr>
<td>1.0 mg/kg/day as initial dose (usually 60 mg/day)</td>
</tr>
<tr>
<td><strong>Adjuvant treatment</strong></td>
</tr>
<tr>
<td>Prednisone in combination with steroid-sparing agents</td>
</tr>
<tr>
<td><strong>Azathioprine</strong></td>
</tr>
<tr>
<td>2–4 mg/kg/day (usually 100–300 mg/day)</td>
</tr>
<tr>
<td><strong>Mycophenolate mofetil</strong></td>
</tr>
<tr>
<td>35–45 mg/kg/day (usually 2–3 g/day)</td>
</tr>
<tr>
<td><strong>Pulse methylprednisolone</strong></td>
</tr>
<tr>
<td>500 mg–1 g/day over 2–3 h, repeated for 3–5 consecutive days</td>
</tr>
<tr>
<td><strong>Cyclophosphamide</strong></td>
</tr>
<tr>
<td>1–3 mg/kg/day (usually 50–200 mg/day)</td>
</tr>
<tr>
<td><strong>Cyclosporine</strong></td>
</tr>
<tr>
<td>3–5 mg/kg/day</td>
</tr>
<tr>
<td><strong>Methotrexate</strong></td>
</tr>
<tr>
<td>2.5–7.5 mg/week (maximum 12 mg/week given over 2 days)</td>
</tr>
<tr>
<td><strong>Plasmapheresis</strong></td>
</tr>
<tr>
<td>Usually 2–3 times a week</td>
</tr>
<tr>
<td><strong>Immunoadsorption</strong></td>
</tr>
<tr>
<td>Various schedule available [99, 100]</td>
</tr>
<tr>
<td><strong>High-dose intravenous immunoglobulin</strong></td>
</tr>
<tr>
<td>0.4 mg/kg/day over 5 days, infused at a rate of not more than 2 mg/kg/min, repeated monthly</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other steroid-sparing agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dapsone</strong></td>
</tr>
<tr>
<td>100–150 mg/day</td>
</tr>
<tr>
<td><strong>Doxycycline or minocycline with or without nicotinamide</strong></td>
</tr>
<tr>
<td>200–300 mg/day or 100–200 mg/day</td>
</tr>
<tr>
<td><strong>Gold</strong></td>
</tr>
<tr>
<td>50 mg/week (initial dose)</td>
</tr>
<tr>
<td><strong>Anti-CD20 antibodies</strong></td>
</tr>
<tr>
<td>375 mg/m² body surface area weekly over 4 consecutive weeks</td>
</tr>
</tbody>
</table>

Key to evidence-based support: (1) good; (2) medium; (3) weak

In BP, the initial dose is usually 0.5–1.0 mg/day (30-60 mg/day), depending on the severity of the disease. Because the disease mainly affects elderly people who are more susceptible to severe complications, it is very important to minimize the total dose and duration of therapy with prednisone.

Epidermolysis bullosa acquissita is often resistant to various therapies. Using corticosteroids alone or in combination with immunosuppressants such as azathioprine, cyclosporine [33, 34], or dapsone [35] has been reported to have some benefit. Mycophenolate mofetil, colchicine [36], plasmapheresis, and IVIG are also reported as effective agents for treating epidermolysis bullosa acquissita [37, 38].

Corticosteroid intravenous pulse therapy: This pulse therapy with methylprednisolone (500–1000 mg/day over a period of 2–3 h, repeated for three consecutive days) is of benefit in rapidly controlling active blister formation in bullous diseases. However, because of its adverse effects, it should be used only in relatively young patients that have high disease activity even after treatment with standard-dose prednisone. After pulse therapy, maintenance doses are usually reduced to the initial dose of prednisone (1 mg/kg/day). For some severe cases, it is also necessary to add immunosuppressive agents such as azathioprine or mycophenolate mofetil at this point as steroid-sparing agents.

The aim of pulse therapy is to achieve more rapid and effective disease control compared with conventional oral corticosteroids in the initial stages of treatment. The main adverse effects include anaphylactic reactions, hypercoagulation, seizures, arrhythmias, and even sudden death. Other side effects are hypertension, hypotension, hyperglycemia, electrolyte shifts, and acute psychosis. Administration over 2–3 h reduces many of the serious adverse effects to some extent.

Immunosuppressants: Immunosuppressants such as azathioprine and mycophenolate mofetil are useful as
steroid-sparing agents. Methotrexate and cyclophosphamide are also used, but less frequently and only in selected cases because of their adverse effects.

**Azathioprine** (2–4 mg/kg/day or 100–200 mg/day): Azathioprine is an antimetabolite agent, a commonly prescribed adjuvant drug for the management of autoimmune bullous disease. The dose is usually given as 2–4 mg/kg/day (or 100–200 mg/day) with prednisone. The optimal dosage can be decided by the measurement of thiopurine methyltransferase (TPMP) levels in patients [39]. Patients with TPMP deficiency cannot metabolize the drug effectively and will develop severe pancytopenia during the first 2 months of therapy. Azathioprine should be avoided in patients with very low TPMP levels [40]. Well-known side effects include hepatotoxicity, neutropenia, and thrombocytopenia. If complete clinical remission is achieved with the combined therapy, the dosage of the immunosuppressive drug is maintained while the prednisone is gradually tapered.

**Mycophenolate mofetil** (35–45 mg/kg/day or 2–3 g/day with prednisone): Mycophenolate mofetil is a relatively new and effective antimetabolite immunosuppressive drug in autoimmune bullous disease. It specifically inhibits activated lymphocytes and has similar action to azathioprine with fewer side effects, especially hepatotoxicity. The daily dose is 35–45 mg/kg/day (or 2–3 g/day; given in divided doses bid) with prednisone. The effect is slow acting; at least 8 weeks are required for clinical and immunological improvement [41, 42]. This option can be considered in severe cases that fail to respond to conventional therapy. Because of its excellent safety profile and efficacy, it may ultimately replace azathioprine as a first-line drug in treating refractory cases. The major side effect is gastrointestinal intolerance, but this improves with dose reduction. A disadvantage of this drug is its high cost.

Azathioprine and mycophenolate mofetil are also reported as successful monotherapy drugs in mild cases [43–45]. A prospective, multicenter, randomized, non-blinded clinical trial compared two parallel groups of patients with pemphigus treated with oral methylprednisolone plus azathioprine or with oral methylprednisolone plus mycophenolate mofetil [46]. The results suggest that mycophenolate mofetil and azathioprine have similar efficacy, corticosteroid-sparing effects, and safety profiles as adjuvant treatments in the treatment of pemphigus vulgaris and pemphigus foliaceus. However, in terms of the rate of remission after 200 days, mycophenolate mofetil treatment induced 90% remission in patients compared with 43% in those receiving azathioprine [46].

**Cyclosporine** (3–5 mg/kg/day with prednisone): Cyclosporine is another immunosuppressive agent with a steroid-sparing effect. The daily dose is 3–5 mg/kg/day with prednisone. A single, randomized, prospective controlled trial comparing oral methylprednisolone 1 mg/kg alone vs. methylprednisolone with cyclosporine 5 mg/kg found no statistically significant difference in outcome measures such as time to healing, complete remission rate, and cumulative corticosteroid dose. The results suggest that there is no apparent benefit of cyclosporine as an adjuvant agent in pemphigus vulgaris when comparing patients treated with corticosteroid alone or with adjuvant therapy, but there are more side effects with cyclosporine [47]. The main side effect is renal toxicity. In the UK, because of the efficacy and adverse events for pemphigus vulgaris patients, it is not recommended as an adjuvant drug [48], but in Japan, because there are some reports suggesting the efficacy of this agent, it is still chosen as a useful drug for the treatment of pemphigus. Empirically, at least in our experience, some cases of epidermolysis bullosa acquisita show fairly good response with cyclosporine.

**Cyclophosphamide**: Cyclophosphamide is a derivative of nitrogen mustard and acts primarily as a DNA cross-linker. It is used as an antineoplastic agent in oncology and is also used in the treatment of autoimmune blistering diseases as a steroid-sparing agent. Cyclophosphamide can be given with daily oral dosing and pulse intravenous dosing schedules. Both dosing schedules should be planned early in the day, with vigorous hydration to minimize the risk of bladder toxicity.

When given as a daily dose with prednisone, 1–3 mg/kg/day (usually 50–200 mg/day) is administered. When given with intravenous pulse corticosteroids, usually three daily doses of 100 mg of dexamethasone or 500–1,000 mg of methylprednisolone are given, with a single monthly dose of cyclophosphamide (500 mg). Dexamethasone–cyclophosphamide pulse therapy at 4-week intervals has been reported in a large case series of Indian patients [49]. The treatment schedule consists of giving 100 mg of dexamethasone on three consecutive days with 500 mg of cyclophosphamide on day 1 and repeating this pulse every 4 weeks. Between cycles, patients receive oral 50 mg of cyclophosphamide daily without corticosteroids. The well-known adverse effects of this pulse therapy are amenorrhea in menstruating females (62%), azoospermia in males,
hemorrhagic cystitis (0.6%), and pituitary-adrenal suppression (55%) [48].

Single, very high-dose immunoablative therapy with 50 mg/kg/day cyclophosphamide for 4 days is also reported as an alternative choice for refractory cases. This high dose of cyclophosphamide eradicates almost all immune-mediated cells without damage to bone marrow stem cells. This is one of the most radical approaches to achieve general immune suppression to reduce pemphigus antibody formation, but has potentially fatal side effects [50, 51].

The drug toxicities include the induction of hemorrhagic cystitis during the period of administration and bladder cancer. Weekly complete blood counts and urinalysis are required. Pulse dosing is usually given with MESNA (2-mercaptosulfonic acid) to reduce bladder toxicity [52]. Because of the severe adverse events, cyclophosphamide should be used only for severe or refractory cases of pemphigus vulgaris that have failed to respond to other conventional therapies.

*Methotrexate*(2.5–5 mg to 12 mg/week): Methotrexate, a folate antagonist, is a potent anti-inflammatory agent when used weekly at low concentrations. The mechanism of the drug is still unclear, but low-dose methotrexate suppresses neutrophil and monocyte chemotaxis, both in vitro and in vivo. Methotrexate was originally reported to have high mortality and morbidity rates in the 1960s to early 1970s because it was used at very high (125–420 mg/week) doses in combination with 40–240 mg/day of prednisolone [53]. Recent studies suggest its efficacy at low doses of 2.5–5.0 mg maximum at 12 mg/week given orally every 12 h for three doses in combination with prednisone when compared with prednisone alone. Methotrexate could be considered as an adjuvant therapy in pemphigus and BP if other established drugs are found inefficient [53, 54], although some reports are contradictory [55]. Methotrexate should not be considered for patients on high-dose prednisone because this combination may be associated with sepsis [56]. The main adverse effects are gastrointestinal intolerance such as nausea, stomatitis, and diarrhea, and hepatic toxicity, anemia, leukopenia, and pulmonary acute hypersensitivity.

*Tetracyclines alone or combined with nicotinamide*: This is a good therapeutic option for BP with mild disease activity because of its low grades of adverse effects [57, 58]. The mechanism of action of tetracyclines in BP may include the inhibition of neutrophils and eosinophil recruitment, blocking of collagenase or proteases, and inhibition of antibody formation, although these mechanisms are highly speculative. The optimum dose is not established. Tetracycline has been used at doses of 500–2,000 mg, doxycycline at 200–300 mg, and minocycline at 100–200 mg, combined with or without nicotinamide 500–2,500 mg, daily. Nicotinamide should be started at a dose of 500 mg daily, then gradually increased to 1,500–2,500 mg daily [59]. The beneficial effect may be observed within 1–3 weeks, but based on our experience, if no apparent clinical improvement is observed within 2 weeks, other treatments should be considered. This therapeutic option can be considered for elderly patients who cannot tolerate conventional therapy with corticosteroids. Tetracyclines should be avoided in patients with renal impairment and doxycycline and minocycline in patients with hepatic impairment. Tetracycline-induced hyperpigmentation (minocycline is the most frequently reported agent) and a few cases of minocycline-associated pneumonia and eosinophilia have been reported. Nausea and dizziness are common adverse effects [58].

*Dapsone*(100–150 mg/day): Dapsone works as an anti-inflammatory agent and is effective in some patients. The mechanism remains unclear, but speculation includes the suppression of the local migration of inflammatory cells. Usually, the initial dose is 100–150 mg/day [60]. Some reports suggest that using dapsone combined with a topical corticosteroid is more effective than using dapsone alone [61, 62]. This drug may be considered for use in cases in which pathologic lesion is characterized by neutrophil infiltration that is not related to bacterial infection such as dermatitis herpetiformis, linear IgA bullous dermatosis, pustular forms of pemphigus foliaceus, and IgA pemphigus. The major adverse events are leucopenia, agranulocytosis, hepatotoxicity, gastric irritation, severe toxic rash, peripheral neuropathy, and acute psychosis.

*Gold*: Gold is known as an adjuvant drug for the treatment of pemphigus and has a steroid-sparing effect when given intramuscularly, with an initially dose of 50 mg/week. This therapy is rarely used today because of its potentially life-threatening side effects.

*High-dose intravenous immunoglobulin (IVIG)*: High-dose IVIG has been proven to be effective for autoimmune diseases, including autoimmune bullous diseases [63]. Compared with all other adjuvant therapies, IVIG is the only immunotherapy for autoimmune diseases without general immune suppression. The mechanism remains unclear, but several speculative mechanisms have been proposed: (1) IVIG increases the catabolism of immunoglobulins, including autoantibodies, as a
response to the pronounced increase in serum concentrations of immunoglobulins [64]; (2) IVIG modulates or suppresses autoantibody production [65]; (3) IVIG has anti-idiotypic activity that is able to neutralize the pathogenic activity of circulating autoantibodies and/or inhibit the binding of autoantibodies to their target autoantigens [65]; (4) IVIG inhibits complement activation; (5) IVIG blocks Fc receptors on macrophages and antigen-presenting cells; and (6) IVIG inhibits proinflammatory cytokine production [66].

The effect of IVIG is considered to be transient and requires continuation of the infusion at least once a month until the disease activity is controlled. As found with plasmapheresis, the effects of IVIG can be enhanced by combination with cytotoxic drugs such as azathioprine and cyclophosphamide. This option is recommended for recalcitrant cases that are resistant to conventional therapies. An advantage of IVIG includes its rapid action to control disease activity without general immune suppression.

There are different protocols for the administration of IVIG. In general, IVIG is either administered at a dose of 400 mg/kg/day over 5 days or 2 g/kg/cycle is given on three consecutive days. One cycle of administration is repeated every 4 weeks. The total duration of treatment of autoimmune bullous disease with IVIG can be at least 2 years. IVIG is reported to be successful when combined with corticosteroids or other adjuvant agents for autoimmune bullous diseases by decreasing titers of circulating autoantibodies [67, 68]. IVIG is reported to be able to induce remission of the disease when used as a single agent [69], whereas other data indicate its ineffectiveness [70]. Recently, a multicenter, randomized, placebo-controlled, double-blind trial proved high-dose IVIG is an safe and effective treatment for those patients who are resistant to conventional therapies [101]. The adverse effects include cardiac arrhythmias, anaphylaxis, and embolism. Before initiating IVIG therapy, it is suggested that serum levels of IgA be checked because patients with low or no IgA have been reported to develop anaphylaxis [71]. Complete blood counts and hepatic and renal function screening for rheumatoid factor and cryoglobulins are recommended. Patients with cryoglobulins have a high risk for the development of acute renal failure. A disadvantage of this treatment is its high cost.

Plasmapheresis: Plasmapheresis is frequently used as an alternative therapeutic option for severe or intractable cases that have not responded or have contraindications to conventional treatment. Plasmapheresis is a method to physically remove circulating pathogenic autoantibodies and has a direct impact on disease activity. The conventional procedure for plasmapheresis is centrifugal plasmapheresis, with the replacement fluid containing albumin. More recently, plasmapheresis with membrane filtration, which more selectively removes immunoglobulins according to their molecular weights, has been developed. More modern procedures such as immunoadsorption using Protein A or tryptophan columns have been reported [72, 73]. Usually, the procedure is done two or three times per week, repeated over a few sessions. The process of plasma exchange effectively reduces the levels of circulating antibodies by filtering the antibodies from the patient’s plasma. However, during the 7–14-day period after plasmapheresis, pathogenic B cells begin to actively produce more autoantibodies, and titers often reach levels comparable to those before plasmapheresis (rebound phenomenon) [73, 74]. Cyclophosphamide is known to prevent the rebound phenomenon in antibody production. A single procedure of plasmapheresis by centrifugation removes about 15% of antidesmoglein IgG autoantibodies from body fluids [75]. Severe infection, allergic reactions, cardiac arrhythmias, and pulmonary embolism should be taken into account as serious complications [76, 77].

Rituximab: This is a chimeric, monoclonal, humanized antibody that targets cells expressing CD20 such as pre-B, immature, and mature B lymphocytes and induces their depletion in vivo. It was originally developed for the treatment of B-cell malignancies [78]. Further studies indicate that rituximab may have a dual mode of action by directly targeting CD20+ B cells and indirectly decreasing the frequency of autoreactive T cells (by the depletion of B cells, which are critical as antigen-presenting cells), which initiate and maintain the autoimmune response in pemphigus [79]. Rituximab reduces circulating B cells and prevents their maturation into antibody-secreting plasma cells. In addition, whether they respond to rituximab or not, all patients show a transitory reduction in B cells that leads to general B-cell dysfunction [80].

The optimum dose for the treatment of autoimmune bullous disease has not been established, but in the majority of case reports, the dosage for malignant lymphoma is used: 375 mg/m² body surface by slow infusion (4–6 h) once weekly for 4 weeks per course, then repeated for several cycles. A phase I/II dose-escalation trial of rituximab used three different treatment doses: a single infusion of 100 mg/m² (low-dose group); a single infusion of 375 mg/m² (intermediate
group); four infusions (one each week) of 375 mg/m² (full lymphoma dose, high-dose group) [80]. This study suggested that a single infusion of 375 mg/m² or 100 mg/m² may be sufficient for inducing B-cell depletion and clinical response, as reported in patients with SLE [80].

There are many reports of successful treatment of patients with refractory pemphigus or other autoimmune diseases [81]. Basically, during this treatment course, all other medications are continued. The treatment was generally well tolerated by patients, and B cell depletion persisted for 6–12 months; the longest case was 3 years. This prolonged effect and disease control can be seen even when using a single course of rituximab infusions at a dose of 375 mg/m² [82].

The clinical response to rituximab is good and is paralleled by a decrease in serum anti-Dsg3 antibodies. The pemphigus antibody decreased and became undetectable in the majority of patients 4 to 10 months after initiation of rituximab therapy [83]. A few investigations of serum levels of autoantibodies revealed an intriguing result: in pemphigus foliaceus, 3–6 months after rituximab infusion, there was a significant reduction in the serum level of anti-Dsg1 IgG [84]. In contrast, other reports found that in patients with mucocutaneous PV, clinical remission was achieved without a decrease in the anti-Dsg3 IgG titer [82, 85]. Non-randomized prospective studies demonstrated that rituximab led to complete remissions in the most of cases of vulgaris and pemphigus foliaceus who are resistant to conventional therapies [102, 103]

There are few reports of successful treatment of refractory cases of epidermolysis bullosa acquisita with rituximab [86]. The management dosage is the same as when treating other autoimmune bullous diseases. With PNP, there have been recent reports suggesting that rituximab is effective in cases associated with non-Hodgkin’s lymphoma [87]. However, others have reported failure in three cases [88].

Side effects, including headache, fever, chills, urticaria, pruritus, and hypotension, are mainly observed during the infusion period. These symptoms are usually mild and can be controlled or prevented by premedication; the infusion reaction can be pretreated with either 40-mg doses of prednisone twice or paracetamol and loratadine without prednisone [80]. Further investigations are needed to establish appropriate premedication in rituximab treatment. However, severe infectious events related to the treatment, including a fatal outcome, have also been reported [89–93]. At this stage, rituximab appears to be an effective and rational treatment for patients with refractory autoimmune bullous diseases that are resistant to conventional therapies with other more common adjuvant treatments.

**7.1.4.2 Topical Treatment**

In mild cases of pemphigus foliaceus with isolated skin erosions, topical corticosteroids may be sufficient to control the disease. Localized BP can be successfully treated with topical corticosteroids alone. Topical corticosteroid is also reported as an effective treatment for both moderate and severe BP [94]. For severe cases, topical antibiotics are used to prevent secondary infection and reduce the pain. It is very important to soak the affected skin to remove the debris and crusts, which can provide a suitable environment for secondary infection. Daily showers or bathing with diluted disinfectant or bacteriostatic solutions is helpful to keep the lesion clean and allow the normal epithelium of the skin to grow. The erosions or painful lesions can be protected by dressing with a light coating of ointment such as Vaseline. Sulfadiazine is effective for the treatment of infectious lesions. Painful mouth or oral lesions respond partially to topical corticosteroids or other topical immunosuppressants. Improved oral hygiene is important to minimize irritation of the lesions. Rinsing the mouth with prednisone gel is helpful. Viscous xylocaine reduces pain, especially before a meal. Rinsing the oral cavity after every meal helps eliminate food debris that may adhere to lesions and thereby prevent their recovery and re-epithelialization. There are a few reports on the effectiveness of topical tacrolimus [95, 96], but its efficacy remains to be further demonstrated.

**7.1.5 Experimental Approaches**

In addition to the above treatments, other experimental approaches for refractory pemphigus or pemphigoid have been reported or proposed. **Immunoadsorption with Protein A or tryptophan:** More modern procedures such as immunoadsorption using Protein A or tryptophan columns have been established for the treatment of pemphigus [72, 73].
The advantages over conventional procedures are: (1) the selective removal of immunoglobulins from the circulation; (2) no requirement for the substitution of plasma components such as human albumin or fresh-frozen plasma; and (3) two or three times more plasma volume per treatment can be processed. Immuno-adsorption selectively removes circulating IgG using extracorporeal immunoabsorption columns with Protein A, which binds to IgG antibodies. Deep vein thrombosis, bradycardia, hypotension, and dizziness have been reported as major adverse events [73]. Antigen-specific removal of pathogenic IgG autoantibodies with recombinant desmogleins has been described using passive transfer mouse models [7, 9].

Antibodies against heavy-chain variable regions: Previous studies using phage display to clone monoclonal antibodies from patients with pemphigus vulgaris demonstrated that a limited number of antibody variable-region genes encode the autoantibody repertoire [97]. On the basis of this, it may be feasible to develop anti-idiotypic antibodies against the variable regions of pathogenic antibodies to block blister formation in pemphigus as a novel variable heavy chain (VH) gene-targeted approach to pemphigus treatment [98].

7.1.6 Complications to Avoid

Because pemphigus is a life-threatening disease and most patients need to take corticosteroids with or without various immunosuppressive agents for a significantly long period of time, it is important to monitor all patients closely for potential side effects. On the basis of our own experiences, the treatment process can be divided into two phases; consolidation and maintenance. Investigations of complete blood cell counts with differential, hematocrit, serum urea, creatinine, electrolytes, liver and kidney function, fasting glucose, serum cholesterol and lipid levels, urinalysis and cultures (including sputum, pharynx, nasal, urine, stool, and skin erosion) are recommended, not only before starting the treatment, but also during the entire treatment process. Monitoring of the serum autoantibody titer by immunofluorescence or ELISA will help as a guide to reduce corticosteroid dosing.

Before starting treatment, confirm the diagnosis of pemphigus (including clinical finding, histopathology, direct immunofluorescence(DIF), indirect immunofluorescence (IIF) and enzyme-linked immunosorbent assay (ELISA). Disease activity should be objectively evaluated with pemphigus disease area index (PDAI) or autoimmune bullous skin disorder intensity score (ABSIS) [104]. Chest X-ray and tuberculin skin test are recommended to evaluate the activity of old tuberculosis. If the patient has old tuberculosis or evidence of exposure to Mycobacterium tuberculosis, prophylactic therapy should be considered. The pharynx, larynx, esophagus and nasal cavities should be examined using an endoscope if the patient has symptoms that suggest the involvement of these areas. A baseline bone density study should be made especially for elder woman to evaluate osteoporosis.

There are also several important points to note in each phase.

1. Consolidation phase (from starting prednisone to successfully control disease activity and start tapering corticosteroid, usually 2 to 4 weeks after initial treatment)

The disease characteristics of patients in this phase are usually treated with high-dose corticosteroids with or without other immunosuppressive agents. β-D-glucan and cytomegalovirus (CMV) antigenemia are useful markers to evaluate opportunistic infection such as bacterial, viral, fungal and Pneumocystis jiroveci.

2. Maintenance phase (Early stage; usually 60-20 mg/day of prednisone with or without immunosuppressive agents. Late stage; 20 mg or less/day of prednisone with or without immunosuppressive agents)

In early stage, corticosteroids are carefully reduced using PDAI or ABSIS. After skin or mucous lesions subsided, antibody titers measured by ELISA (initially 1×/1-2week, then 1×/month) are a useful indicator to evaluate the disease activity. β-D-glucan and CMV

Take-Home Message

The primary goal of treatment is to rapidly and effectively suppress disease activity without any serious side effects. It is advised to pay attention to osteoporosis prophylaxis, gastric protection, cardiovascular function, and infection risk. The aim is complete remission, with treatment discontinued or at minimum doses.
antigenemia in addition to routine blood test are useful to monitor opportunistic infection and other complications. In addition, the following tests are suggested. e.g., TPMP (thiopurinemethyl transferase concentrations) for patients who take azathioprine; anticoagulant system, including coagulant factors, for patients who take pulse therapy; cardiac function, including blood pressure, ECG and echocardiogram, for patients who are considered to take cyclophosphamide pulse therapy; chest X-ray and body CT to rule out internal malignancies; reiculocyte count for patient who take dapsone. A checklist is given in Table 7.1.2.

### Table 7.1.2 Check list for treatment of pemphigus

<table>
<thead>
<tr>
<th>Check points before treatment starts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Essential points</strong></td>
</tr>
<tr>
<td>Confirm the diagnosis of pemphigus (including clinical finding, histopathology, direct immunofluorescence (DIF), indirect immunofluorescence (IIF) and enzyme-linked immunosorbent assay (ELISA))</td>
</tr>
<tr>
<td>Use PDAI* or ABSIS** to evaluate disease severity</td>
</tr>
<tr>
<td>Urine, complete blood count with differential, liver, kidney function, cholesterol and lipid level, diabetes by measuring fasting blood glucose and serum HbA1c, CRP</td>
</tr>
<tr>
<td>Chest X-ray, body weight and entire medical status, including diabetes, hypertension, gastric condition, past history of gastric ulcer, cataracts, and osteoporosis</td>
</tr>
<tr>
<td>Baseline bone density study, especially for elder woman (regularly once or twice per year)</td>
</tr>
<tr>
<td><strong>Suggested points</strong></td>
</tr>
<tr>
<td>Eindoscopic evaluation for pharynx, larynx, esophageal lesion</td>
</tr>
<tr>
<td>TPMP (thiopurinemethyl transferase concentration) when using azathioprine</td>
</tr>
<tr>
<td>History of old tuberculosis and tuberculin skin test; if the patient has old tuberculosis or evidence of exposure to Mycobacterium tuberculosis, prophylactic therapy should be considered</td>
</tr>
<tr>
<td>Baseline culture (skin, pharynx, urine, stool)</td>
</tr>
<tr>
<td>Evaluate immune system including serum immunoglobulin level and CD4/CD8</td>
</tr>
<tr>
<td>Evaluate underlying disease including thymoma or other malignancy using echogram, CT or PET</td>
</tr>
<tr>
<td>Ophthalmological evaluation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Check points during maintenance phase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Essential points</strong></td>
</tr>
<tr>
<td>Regularly do complete blood test with differential, HbA1c, liver and kidney function, serum lipid level, CRP and immunoglobulin level</td>
</tr>
<tr>
<td>Circulating anti-desmoglein 1 and/or 3 autoantibody titer (initially 1×/1-2week, then 1×/month)</td>
</tr>
<tr>
<td><strong>Suggested points</strong></td>
</tr>
<tr>
<td>Chest X-ray 1×/month to evaluate pneumonia</td>
</tr>
<tr>
<td>βD-glucan, CMV*** (1×/1-2month) antigenemia for evaluate fungal infection and Pneumocystis jiroveci</td>
</tr>
<tr>
<td>Administration of sulfa drug (Co-trimoxazole, a combination of trimethoprim and sulfamethoxazole) for prevent Pneumocystis jiroveci pneumonia when prednisone is given above 20 mg/day</td>
</tr>
<tr>
<td>Rinsing the mouth with antifungal solution to prevent oral candidiasis</td>
</tr>
<tr>
<td>Consultation with dentist to evaluate oral hygiene for severe oral lesions</td>
</tr>
</tbody>
</table>

*PDAI; pemphigus disease area index  
**ABSIS; autoimmune bullous skin disorder intensity score  
***CMV; cytomegalovirus
7.1.7 Global Variation

7.1.7.1 Choice of Adjuvant Therapy

Corticosteroids are the mainstay for the treatment of autoimmune bullous diseases and are widely accepted around the world. The choice of adjuvant therapy is largely dependent on the insurance system, which plays an important role in making treatment available to patients. New drugs, including mycophenolate mofetil or rituximab, are very expensive. In the USA, treatment with such drugs depends on the level of insurance coverage; in the UK, it depends on local government decisions; and in Japan, new drugs need independent approval through clinical trials conducted in Japan (approximately 30% of drugs available in the USA are not available in Japan). This makes it difficult for Japanese doctors to use new drugs such as mycophenolate mofetil or rituximab. This variation makes it difficult to make consensus guidelines for treatment protocols in autoimmune bullous diseases.

Even though there are many variations in the treatment of autoimmune blistering disease, the most important factor is how to reduce the disease activity rapidly using different agents or options. The final goal of treatment is common and clear: suppress disease activity quickly with minimal side effects to induce complete remission.

7.1.7.2 Corticosteroids Alone or In Combination with Immunosuppressants

It is difficult to predict the course of activity at initial stages of the disease. It is also difficult to determine whether an individual case becomes treatment-resistant. For example, when patients have a relatively mild form of oral-dominant pemphigus vulgaris, it is not clear whether treatment should be started with corticosteroids alone or in combination with an immunosuppressive agent. Corticosteroids with an immunosuppressive agent would give higher remission rates over shorter treatment durations. However, for some patients, immunosuppressive agents may be unnecessary. Some doctors do not use adjuvant therapies unless the case needs to use minimal doses of corticosteroid because of some complications or the disease is uncontrolled with corticosteroids alone or relapses during corticosteroid dose tapering. Other doctors use both the agents from the beginning. In most cases, the decision is made based on the experiences of individual doctors.

References

7.1 Acquired Bullous Disease


7.2.1 Systemic Lupus Erythematosus

**Key Features**

- A connective tissue disorder characterized by immunological hyperactivity
- Inflammation in multiple organs including skin and kidney
- Three forms of lupus erythematosus (LE) - specific skin lesion: acute cutaneous LE, sub-acute cutaneous LE, and chronic cutaneous LE/discoid lupus erythematosus
- Specific autoantibodies such as antidouble-stranded DNA antibody and anti-Sm antibody
- Various nonspecific skin lesion or autoantibodies
- Sun exposure, infection, and drugs may induce the symptoms

7.2.2 Etiology and Pathophysiology

Systemic lupus erythematosus (SLE) is a multisystem autoimmune connective tissue disorder characterized by immunological hyperactivity and various clinical features [1–3]. The average age at onset is in the range of 20–40 years and female to male ratio is 9:1. The overall average incidence of SLE has been estimated to range between 18 and 76 cases per million population per year. Although the pathogenesis of SLE remains unclear, its etiology has been considered to be dependent on genetic and environmental factors.

Genetic factor: A genetic component for SLE has been suggested by concordance in monozygotic twins and familial associations. SLE has been most strongly associated with HLA-DR2 and –DR3 haplotype. It has been reported that genetic deficiencies of complement components are associated with the development of SLE. Recent findings indicate that mutation of various disease susceptibility genes may induce disease expression via affecting both the innate and adaptive immune systems.

Environmental factor: Environmental factors likely affect the disease expression in the genetically susceptible host. Viral infection and endogenous retrovirus are candidates that induce the abnormal immune function possibly due to the cross-reactivity with autoantigen. Ultraviolet radiation can be an initiating factor of disease development of SLE. Certain drugs (e.g., procainamide, hydralazine, isoniazid, chlorpromazine, and dilantin) have also been implicated in inducing clinical features of SLE.

Innate immunity: Recent studies indicate that the innate immune system might promote an adaptive immune response in SLE [4]. Toll-like receptors have been considered to have critical roles in the process from innate immunity to adaptive immune response in SLE. Infection can be a trigger for the onset or exacerbation of SLE, and Toll-like receptors may play central roles in this connection. It has been demonstrated that expression levels of genes regulated by type I interferons (IFNs) are augmented in peripheral blood leukocytes of SLE. While myeloid and plasmacytoid
dendritic cells have been considered as potential sources of IFNs, immune complexes containing nucleic acid (e.g., viral nucleic acid) also have an ability to produce IFNs. Interestingly, these chromatin-containing complexes can also stimulate autoreactive B cells.

Lymphocytes: Recent findings clarified that B cells have multiple functions such as antigen-presentation, T-cell activation, cytokine production, and antibody production. B cell depleting therapies using anti-CD20 chimeric monoclonal antibody rituximab have shown dramatic efficacy for resistant SLE or lupus nephritis in several open studies [5]. Therefore, B cell hyperactivity or altered B cell function may be a central component for the pathogenesis of SLE. In addition, altered T-cell activation or the interaction between T and antigen-presenting cells are probably contributing to the development of this disease.

7.2.3 Clinical Characteristics and Diagnosis

7.2.3.1 Clinical Features

SLE can induce inflammation or tissue injury in any organ. It ranges from mild clinical features such as skin or joint lesion to severe organ involvement affecting kidneys or central nervous system. A patient is diagnosed with SLE if he or she fulfills at least four of the following 11 classification criteria of American College of Rheumatology [6]: (1) malar rashes (non-scarring erythema across the bridge of the nose and cheeks), (2) discoid rash (scarring erythema), (3) photosensitivity, (4) oral ulcers, (5) arthritis, (6) serositis, (7) renal involvement, (8) central nervous system involvement (seizures or psychosis), (9) hematologic abnormalities (hemolytic anemia, leukopenia, thrombocytopenia), (10) immunological abnormalities (antIDDLE DNA, anti Sm or antiphospholipid antibodies), and (11) antinuclear antibody. Nonspecific symptoms such as fatigue, malaise, fever, and bodyweight loss are often observed. Various other manifestations including myositis, lymphadenopathy, pneumonia, and vasculitis may develop in some of the patients. The SLE disease activity index (SLEDAI), the British Isles lupus assessment group (BILAG), and the systemic lupus activity measure (SLAM) are representative means to evaluate the disease activity [7–9].

7.2.3.2 Skin Lesion

The cutaneous lesions specific for LE are found in patients with SLE and other patients (cutaneous LE). LE-specific skin lesions or cutaneous LE can be further divided into three types, based on the clinical appearance and histopathology. Various nonspecific LE lesions are also found in patients with SLE. LE-specific skin lesion (disease) includes acute cutaneous LE (ACLE), subacute cutaneous LE (SCLE), and chronic cutaneous LE (CCLE)/discoid lupus erythematosus (DLE).

- ACLE: The classic malar (butterfly) rash or extensive erythema over the extensor aspects of the arms and hands is observed in SLE patients in parallel with the disease activity (Fig. 7.2.1). This acute, edematous, erythematous eruption sometimes develops after exposure to sunlight. Histopathologically, liquefaction, degeneration, and mild atrophy are found in the epidermis. Dermal changes include edema and sparse mononuclear cell infiltration usually limited to the perivascular areas and adnexal structures in the upper dermis. A band of immunoglobulin deposition is commonly seen along the thickened dermoepidermal junction.

- SCLE: SCLE is a symmetric, widespread, superficial form of cutaneous LE and develop in predominantly sun-exposed areas. This lesion is considered to be the intermediate eruption between ACLE and the CCLE/DLE. The lesions originate as erythematous papules or small plaques with a scaly surface, producing a psoriasiform pattern (papulosquamous type) or may expand peripherally making annular lesions and show polycyclic configurations (annular/polycyclic type). About half of patients with SCLE do not fulfill the classification criteria of SLE. SCLE lesion is especially found in patients with the antibody to Ro/SS-A and/or La/SS-B. The skin lesions of neonatal LE share many features with SCLE.

- DLE: The skin lesions of DLE, chronic skin form of LE, are coin-shaped discrete erythematous plaques with a well-formed adherent scale (Fig. 7.2.2). These lesions heal leaving atrophic scar. DLE lesions are most frequently encountered on the
7.2 Connective Tissue Diseases

Sun-exposed lesion of skin and mucous membrane. Lesions in the scalp leave irreversible alopecia due to the destruction of follicles. While DLE can be localized or generalized, generalized eruption associates with systemic features and serologic abnormalities of LE. Histopathological findings of DLE include prominent hyperkeratosis, well-developed follicular plugging, liquefactive degeneration of the epidermal basal cell layer, and thickening of epidermal basement membrane with immune deposits. A mononuclear infiltrate localized to periappendageal and perivascular areas are also found in all the layers of dermis. Approximately, 25% of patients with SLE have DLE lesions during their clinical course, and such patients tend to have less severe systemic symptoms. LE panniculitis or lupus profundus is a subtype of DLE that is characterized by inflammation of subcutaneous tissues. These lesions are found as subcutaneous nodules with or without surface change that develop predominantly on the head, face, upper limbs, thighs, and hip.

- Nonspecific LE lesion: Raynaud’s phenomenon is found in more than 50% of patients. Various vascular lesions such as livedo, urticarial vasculitis, cutaneous vasculitis, and digital ulcer can develop in patients with SLE.

### 7.2.3.3 Laboratory Findings

Almost all patients with SLE have detectable antinuclear antibodies. Antibodies against dsDNA and an acidic nuclear protein (Sm) are most specific autoantibodies for SLE. Antibodies against U1 ribonucleoprotein (U1 RNP) are found in SLE patients who have overlapping features of myositis and systemic sclerosis. Patients with SLE usually have other autoantibodies such as antinuclear-stranded DNA, LE cells, anti-SS-A (Ro), or anti-SS-B (La) antibodies. The titer of anti-dsDNA antibodies generally associates with the activity of SLE and the development of lupus nephritis. Patients with antiphospholipid Abs have a risk for antiphospholipid syndrome characterized by arterial and venous thromboembolism and recurrent spontaneous abortions. Decreased serum complement levels are generally associated with active SLE, especially in patients with lupus nephritis. Also, leucopenia, hypergammaglobulinemia, increased erythrocyte
sedimentation rate, proteinuria, and hematuria can be found in patients.

7.2.4 General Therapeutic Outline

All patients should receive guidance for the protection from sun exposure including the use of sunscreens. The management should be determined in individual patient, dependent on the degree and severity of specific symptoms and/or organ involvement. In general, topical therapy is the first choice for skin-restricted lupus. Corticosteroids and antimalarials provide the therapeutic foundation for patients with SLE. Azathioprine and cyclophosphamide are popular as immunosuppressive drugs for more severe manifestations.

7.2.5 Current Established Therapies

7.2.5.1 Topical Therapy of the Skin

Patients with isolated cutaneous lesions including DLE may be appropriate for isolated topical therapies. Local corticosteroids treatment is useful and is more effective in combination with oral antimalarial therapy. Recent small case studies have shown that topical administration of tacrolimus and pimecrolimus is effective [10].

7.2.5.2 Nonsteroidal Systemic Therapy

Nonsteroidal anti-inflammatory drugs (NSAIDs) are usually used for the treatment of mild LE symptoms such as musculoskeletal manifestations, mild serositis, and fever. Antimalarial drugs are frequently effective for patients with mild SLE, especially for those with cutaneous and musculoskeletal manifestations. Antimalarials are particularly useful in patients with SCLE, widespread DLE, or lupus profundus. The antimalarials most commonly used are hydroxychloroquine (200 mg/day) or chloroquine (200 mg/day). Patients with refractory cutaneous LE (SCLE more than DLE) may respond to dapsone (Dapsone) in oral doses of 25–100 mg/day.

7.2.5.3 Systemic Corticosteroids

Oral corticosteroids therapy has both anti-inflammatory and immunosuppressive effects and is a standard therapy for patients with moderate and severe SLE or in those in whom NSAIDs and/or antimalarial drugs are ineffective. The dose of corticosteroids varies depending on the targeted organ or manifestation in each patient (prednisolone ~ 1 mg/kg). Pulse steroids therapy (intravenous methylprednisolone 1 g × 3 days) may be used for severe or life- or organ-threatening symptoms such as active lupus nephritis and acute central nervous system lesion. After the disease activity is controlled, tapering of the corticosteroid is initiated. However, many patients have to continue low-dose corticosteroids (~10 mg/day) to prevent recurrence.

7.2.5.4 Immunosuppressive Agents

Immunosuppressive drugs such as azathioprine and cyclophosphamide are needed to gain control of the disease in patients with life- or organ-threatening complications, as well as for steroid tapering [11]. Oral azathioprine is the most popular immunosuppressive drug for the treatment of SLE. Combination therapy with pulse intravenous cyclophosphamide and oral corticosteroids has been reported to be effective in severe manifestation, such as proliferative lupus nephritis and central nervous system lupus. Recent studies have shown that short courses of low-dose pulse cyclophosphamide followed by azathioprine achieve results similar to the usual monthly pulse cyclophosphamide therapy with less toxicity in patients with lupus nephritis [12]. The principal limitations to cyclophosphamide are its adverse events, including infertility, hemorrhagic cystitis, malignancy, cytopenia, and infection. Although cyclosporine A has been used successfully as a steroid reducing drug in SLE, its use is limited by its side effects, especially renal impairment. Mycophenolate mofetil, an inhibitor of
purine synthesis, blocks the proliferation of T and B lymphocytes. Mycophenolate mofetil has shown favorable results similar to cyclophosphamide in randomized trials as both induction and maintenance therapy for severe lupus nephritis [13–15]. Considering the numerous toxicities of cyclophosphamide, mycophenolate mofetil may be regarded as an appropriate alternative for treatment of severe SLE.

### 7.2.5.5 Other Therapies

Plasmapheresis can be used for the management of severe SLE or its complications [16]. Although its mechanism of action is unclear, it may be due to the physical removal of pathogenic autoantibodies and circulating mediators such as activated complement components or cytokines.

Intravenous immunoglobulins can be used for the treatment of refractory SLE, although there have been no large randomized trials. This therapy is especially useful in patients who have thrombocytopenia or active LE with immunosuppressant risk. Although there are many possible explanations for why this agent works, the effects on Fcγ receptor is probably dominant. The main limitation of this agent is high cost.

### 7.2.6 Experimental Approaches

Rituximab is a chimeric monoclonal antibody directed against human CD20 on B cells and their precursors but not against plasma cells. Rituximab is widely used in the management of lymphoma and is relatively safe and well tolerated. Several open trials for SLE or lupus nephritis have shown dramatic and long-lasting remissions in patients who were previously unresponsive to conventional immunosuppressive agents [17–19]. Although the exact mechanism of action of B-cell depletion in SLE remains unclear, rituximab therapy may be a new option for lupus patients resistant to conventional treatments. Randomized controlled trials to confirm the evidence of the efficacy of rituximab are ongoing in SLE.

Immunoablation followed by autologous hematopoietic stem cell transplant (HSCT) has been explored in patients with severe systemic lupus [20]. Although there are numerous reports demonstrating favorable results, further studies will be needed to confirm the remission or mortality rate.

New strategies under development include: interruption of the T-B-cell collaboration (e.g., cytotoxic T lymphocyte-associated antigen 4-Ig (CTLA4-Ig)), B-cell targeting by withdrawal of survival or proliferation factors (e.g., antibodies to B cell-activating factor (BAFF), transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI)–Ig), or targeted therapy against B cells themselves (Abs against CD19 or CD22), interruption of complement-mediated inflammation (e.g., anti-C5a antibodies), and cytokine-targeting agents (e.g., antibodies against the interleukin-6 receptor) [21].

### 7.2.7 Complications to Avoid

Life-threatening complications such as hemophagocytic syndrome, thrombotic thrombocytopenic purpura, or hemolytic uremic syndrome may develop in patients with SLE. Disease exacerbation during pregnancy or after delivery is common in SLE. Serious infection should be cared in patients receiving corticosteroids or other immunosuppressive agents. Dietary life or appropriate drugs should protect side effects of corticosteroids including osteoporosis, diabetes, and hyperlipidemia.

### Take Home Message

Corticosteroids and hydroxychloroquine provide the therapeutic foundation, and immunosuppressive agents are added for severe manifestations. B-cell-directed therapy may be a promising therapeutic strategy for refractory SLE.

### 7.2.8 Global Variations

There is little global variation in treatment.
7.2.9 Systemic Sclerosis

Key Features

- A chronic, systemic disease characterized by tissue fibrosis, vascular injury, and autoantibody production
- Classified into two disease subsets by the extent of skin sclerosis: diffuse cutaneous systemic sclerosis (SSc) and limited cutaneous SSc
- Patients with anticentromere antibody usually exhibit limited skin sclerosis and increased risk for pulmonary arterial hypertension
- Patients with antitopoisomerase I antibody frequently show diffuse skin sclerosis and severe pulmonary fibrosis
- Anti-RNA polymerases antibody associates with severe skin sclerosis and renal crisis

7.2.10 Etiology and Pathophysiology

SSc is an autoimmune rheumatic disease characterized by fibrosis and vascular injury in the skin and internal organs [22, 23]. SSc is a rare disease, with an incidence between 2.7 and 22.8 per million population per year [24]. The average age at onset is in the range of 30–50 years [25].

The etiology and pathogenesis of SSc remains unknown. Three facets of the disease typify the clinical features of SSc: vascular damage, excessive collagen deposition, and immunological activation [26]. Additionally, these clinical features are likely to be interrelated to each other. Genetic and environmental factors play some role in the development of the disease. Choctaw American Indians have a high incidence of SSc and inherited a common haplotype [27, 28], making them susceptible to SSc. The SSc-specific autoantibodies are detected in different frequencies in each ethnicities and the diversity is associated with varied HLA. Possible triggers of this disease are viral infections and exposure to chemicals such as vinyl chloride, silica, and organic solvents.

Vascular injury: Clinical manifestations of vascular abnormality include Raynaud’s phenomenon, digital ulcers, nail fold bleeding, pulmonary hypertension, and renal crisis [29]. The typical vascular abnormality is the proliferation of the vascular intimae, which resulted in the inadequate blood flow. Since Raynaud’s phenomenon usually antedates to other clinical symptoms and induces tissue hypoxia, endothelial injury may be the first event of the disease. Then, profibrogenic cytokines produced by platelets and inflammatory cells may induce the tissue fibrosis.

Tissue fibrosis: Tissue fibrosis such as skin sclerosis and pulmonary fibrosis is the most characteristic feature of SSc. Tissue fibrosis results from excessive accumulation of collagens and other extracellular matrix proteins. Fibroblasts from SSc patients show augmented collagen synthesis probably due to both intrinsic abnormalities and increased stimulation by profibrogenic cytokines from other cells and fibroblasts themselves. Among various cytokines, transforming growth factor (TGF-β), platelet-derived growth factor (PDGF), connective tissue growth factor (CTGF), interleukin (IL) -4, or IL-6 have been considered to play central roles in this process of SSc [30–32]. TGF-β stimulates fibroblasts and induces the production of collagen and matrix proteins. Fibroblasts from SSc patients show augmented expression of TGF-β receptors reflecting enhanced TGF-β signaling. TGF-β can also stimulate CTGF production by fibroblasts, vascular smooth muscles, and endothelial cells. Since CTGF can stimulate its own synthesis and collagen production, CTGF may be critical to maintain the collagen overproduction in SSc.

Immunological activation: Immunological activation in SSc is likely a key inducer of vascular abnormalities and tissue fibrosis. A number of findings in SSc patients or SSc mouse model have demonstrated that tissue infiltrating immune cells including T cells and cytokines (e.g., IL-4) released from these cells are critical for the development of tissue fibrosis [33, 34]. Furthermore, recent studies have shown that B cell abnormalities are detected in SSc patients and mouse model of SSc [31, 35, 36].

7.2.11 Clinical Characteristics and Diagnosis

7.2.11.1 Diagnosis

The scleroderma classification criteria of the American College of Rheumatology has been used for diagnosis [37]. The major criterion is skin sclerosis proximal to
Connective Tissue Diseases

7.2 Connective Tissue Diseases

7.2.11.2 Classification

Patients with SSc are classified, by the extent of skin affected, as having diffuse cutaneous SSc (dcSSc) or limited cutaneous SSc (lcSSc) [38]. That is, patients with skin thickening proximal to the elbows and knees are considered to have dcSSc (Fig. 7.2.3) and others are classified as lcSSc patients (Fig. 7.2.4). This classification is important since the clinical course is significantly different between both disease subsets (Fig. 7.2.5) [39].

- dcSSc: Most patients with dcSSc show the rapid progression of skin sclerosis (within ~4 years from the onset), followed by regression of skin thickening. In parallel with the development of skin sclerosis, patients with dcSSc frequently develop the involvement of internal organs such as lung, gastrointestinal tract, muscle, heart, and kidney [40]. Since renal crisis has become a treatable complication, pulmonary fibrosis in addition to pulmonary arterial hypertension is now the most frequent cause of death in SSc. The most common symptoms of pulmonary fibrosis are dyspnea on exertion and dry cough. The application of high-resolution computed tomography scanning of the lungs has been of much use for assessing the lung lesion. Patients with dcSSc...
M. Hasegawa and S. Sato develop mask-like faces with small oral aperture. Finger contractures often occur secondary to skin sclerosis. Skin ulcer or gangrene especially in fingers is also a frequent complication. Pigmentation and hypopigmentation of the skin may be seen at the lesional skin. Nail fold bleeding that is punctate bleeding spots observed by naked eyes is frequently detected in both dcSSc and lcSSc.

- lcSSc: In contrast to dcSSc, patients with lcSSc have an indolent course, often with years of antecedent Raynaud’s phenomenon. Patients with lcSSc show favorable prognosis, if they do not develop severe pulmonary arterial hypertension. Patients with lcSSc usually exhibit swollen fingers, digital ulcers, telangiectasias, or esophageal symptoms. Subcutaneous calcinosis can also be found. Characteristic telangiectasias are frequently found in the skin of lcSSc, although they are also present in dcSSc patients with long disease duration.

### 7.2.11.3 Autoantibody

More than 90% of patients have detectable antinuclear antibodies. The detection of SSc-specific autoantibodies is useful for predicting clinical features or prognosis [41], although they are not likely playing a direct role in the pathogenesis of the disease. In general, anticientromere antibody is seen in patients with lcSSc. About 70% of patients with antitopoisomerase I antibody develop dcSSc, although other patients show clinical features of lcSSc. Patients with anti-RNA polymerases antibody have remarkable skin sclerosis and the high frequency of renal crisis (~25%) [42]. However, patients with anti-RNA polymerases antibody involve lung fibrosis that is milder than that of patients with antitopoisomerase I antibody. Therefore, recent prognosis of these patients is better than that of patients with antitopoisomerase I antibody.

### 7.2.11.4 Clinical Parameters

Assessment of disease activity or severity of SSc is difficult. Possible clinical parameters include skin score, health assessment questionnaires modified for SSc, oral aperture, hand extension, and finger flexion. The degree of skin thickness is often measured using the modified Rodnan skin thickness score technique [43]. The examiner pinches the patient’s skin at 17 sites, scoring each area from 0 to 3 (0=normal skin; 3=severe thickening) and then totalizing the score, giving a maximum score of 51. Recently, a quantitative measure method of the disease severity has been developed that assess the scale of severity of each major organ involvement (grade 0–4) [44].

### 7.2.12 General Therapeutic Outline

No therapies have been proven to be effective for all features of the disease; the treatment should be determined in each patient dependent on the targeted organ and specific pathogenic aspects such as endothelial cell damage, fibrosis, and immune activation.

Disease-modifying therapy should be started especially at early stage (the first 3 years of disease) of dcSSc patients, otherwise the rapid progression of skin sclerosis or visceral change will induce irreversible disturbance. The progression of skin thickening is rapid in early dcSSc, extending proximally on the arms and legs, sometimes but not always affecting the trunk, within several months. Internal organ involvements are frequent in early dcSSc and especially occur during the first 3 years of disease.

### 7.2.13 Current Established Therapies

#### 7.2.13.1 Vascular Injury

Patients should receive instruction to avoid cold stimulus and smoking. Although the calcium-channel blockers are most popular for Raynaud’s phenomenon, other vasodilators including nitrates (topical and oral) and sympathetic agents have also been used [26]. Intravenous vasodilating prostaglandins reduce the severity and frequency of Raynaud’s phenomenon and are most helpful for treating critical ischemia. Sildenafil, a phosphodiesterase 5 inhibitor, has also shown some effectiveness in a small placebo-controlled trial of patients with secondary Raynaud’s disease resistant to multiple therapies [45]. A recent study has demonstrated that bosentan, an oral endothelin antagonist, prevents the relapse of digital ulcers [46]. The important thing is that digital gangrene should be treated with conservative medical management but not surgical amputation in SSc.
The isolated pulmonary artery hypertension occurs in up to 10% of patients with lcSSc and a smaller proportion of those with dcSSc. Secondary pulmonary hypertension associated with pulmonary fibrosis is found especially in dcSSc patients with severe pulmonary fibrosis. Patients with SSc should be monitored regularly for estimated pulmonary artery pressure using doppler echocardiography, and heart catheterization is needed in some situation. Epoprostenol, treprostinil, and iloprost are effective for pulmonary artery hypertension via supplying prostacyclin. Sildenafil increases amounts of nitric oxide and dilates pulmonary artery [47]. Bosentan is effective for pulmonary artery hypertension by blocking endothelin-1 A and B receptors in patients with SSc. Other endothelin inhibitors such as sitaxsentan and inhaled nitric oxide are being investigated [48]. Oral anticoagulation and long-term and low-dose oxygen can be helpful for the treatment of pulmonary artery hypertension.

Patients at high risk for renal crisis are those with early dcSSc with rapidly progressive skin sclerosis, new cardiac problems, recent high-dose corticosteroid use, or the anti-RNA polymerases antibody [49]. Patients at risk should be instructed to check their blood pressure. At onset, patients show remarkably elevated blood pressure, with retinopathy and signs of renal injury, including blood and protein in the urine. Renal crisis used to be the most common cause of death. However, angiotensin-converting enzyme inhibitors have dramatically improved the survival [49, 50].

### 7.2.13.2 Tissue Fibrosis

Most popular drug has been D-penicillamine for treating skin sclerosis in SSc. However, a recent controlled study of D-penicillamine could not detect a significant difference between high and low doses, certainly providing no justification for using high doses [51]. At this time, strategies to reduce fibrosis directly have been disappointing but new strategies against fibrosis are under development.

Immunological activation likely induces vascular injury and fibrosis in SSc. Therefore, several novel therapies are targeting immunological abnormalities. Two small, randomized placebo-controlled studies of methotrexate have shown favorable results [52, 53]. Although a control trial of cyclosporine A has shown a significant effect on skin sclerosis, some side effects for kidney were observed [54]. Recently completed double blind controlled trials of cyclophosphamide (oral or parenteral) in addition to corticosteroids for alveolitis in patients demonstrated that these therapies are significantly effective for improving alveolitis or skin sclerosis [55–57].

### 7.2.13.3 Other Features

Involvement of the gastrointestinal tract, especially the esophagus, is extremely frequent in SSc. Clinical benefit is obtained from acid-suppressive therapies, and the effect of proton-pump inhibitors is remarkable.

### 7.2.14 Experimental Approaches

One of the most aggressive approaches to SSc therapy is the use of immunoablation with autologous peripheral stem cell reconstitution [58]. Randomized controlled trails to address the effectiveness and toxic effects are in progress.

Several candidate approaches are directed against TGF-β, its downstream signaling pathways or secondary mediators [59, 60]. Although there has been one trial of systemic anti-TGF-β1 neutralizing antibody treatment for SSc, it was not able to detect a significant effect [61]. In vitro data and findings in mouse model suggest that imatinib, an effective antileukemic agent, blocks TGF-β-mediated tissue fibrosis via inhibiting c-Abl [62].

Recent studies have revealed that B cells play a critical role in some systemic autoimmune disorders, and various B cell-targeted therapies have been under development. B cell depleting therapy using rituximab (anti-CD20 monoclonal antibody) has been demonstrated as being effective for rheumatoid arthritis and SLE. However, the utility of B cell-targeted therapy remains unclear in SSc [63].

### 7.2.15 Complications to Avoid

Lung cancer is disproportionately frequent, typically associated with long-standing pulmonary fibrosis. Aspiration pneumonia due to dysphasia should be avoided.
There is little global variation in treatment.

### 7.2.17 Dermatomyositis

Polymyositis (PM) or dermatomyositis (DM) is an autoimmune connective tissue disease in which characteristic patterns of inflammatory injury occur in striated muscle [3, 23, 64, 65, 99]. The presence of characteristic cutaneous features such as heliotrope rash or Gottron’s papule/sign distinguishes DM from PM. The estimated incidence of DM/PM ranges from 2 to 10 cases per million per year. The overall female: male incidence ratio is 2–3:1. Most adult cases occur between the ages of 30 and 50 years. Childhood cases peak in prevalence between the age of 7 and 15 years.

Although the pathogenesis remains unknown, it is likely that chronic immune activation following exposure to environmental factors plays a crucial role in genetically susceptible individuals. The occurrence of PM/DM in monozygotic twins and first-degree relatives of cases supports a genetic background, at least in some families. Specific HLA subtypes are believed to increase the risk of developing PM and DM. Especially, association with HLA-B8, DR3, DRB1, and DRw52 has been reported in patients with PM/DM [66–68]. Environmental factors have been considered as disease triggers. There is some evidence to link PM/DM to a viral etiology, especially in children. Disease onset is more frequent in the winter and spring season, especially in childhood, possibly reflecting prior infection [69, 70]. Serum antibodies to Coxsackie B viruses are more frequent in patients with childhood DM compared with controls with juvenile rheumatoid arthritis [69].

Several kinds of myositis-specific autoantibodies are detected in serum from DM/PM patients. Especially, patients with anti-aminoacyl-tRNA synthetase (antisynthetase) autoantibody are said to have antisynthetase syndrome [71]. Whether these autoantibodies are pathogenic or just epiphenomenon is unknown. The etiology of the link between malignancy and the development of DM remains unclear. However, the paraneoplastic theory appears most likely, since the disease activity of myositis usually improves by the treatment of cancer and gets worse by the recurrence of the tumor [99].

### 7.2.19 Clinical Characteristics and Diagnosis

#### 7.2.19.1 Diagnostics and Classification

Bohan and coworkers [72, 73] have classified PM/DM into the following five clinical subsets: (I) PM, (II) DM, (III) PM or DM associated with malignancy, (IV) Childhood PM or DM, and (V) PM or DM with other connective tissue disorders. Euwer and Sontheimer [74] have added a sixth subset as amyopathic DM. The
essential elements of classification criteria are (1) proximal muscle weakness on physical examination, (2) increased serum muscle enzymes, (3) abnormal electromyogram, (4) muscle biopsy consistent with myositis, and (5) the characteristic rash of DM. Depending on these elements, definite (all of (1)–(4)), probable (any three of (1)–(4)), and possible (any two of (1)–(4)) PM have been defined. DM is diagnosed when PM is present associated with (5). Some patients may present with the typical biopsy-confirmed cutaneous manifestation of DM and no muscle involvement (no proximal muscle weakness as well as normal serum muscle enzyme levels). These patients are called as amyopathic DM patients if these findings have continued for 2 years. Most of amyopathic DM patients have a good prognosis, but some may develop malignancy or interstitial pneumonia [75].

### 7.2.19.2 Clinical Features

**General features**

Fatigue is a prominent complaint in patients with PM/DM. Fever is more commonly observed in children, but also in adults with active myositis or interstitial pneumonia. Body weight loss may be seen as a result of systemic inflammation, malignancy, or poor caloric intake due to esophageal dysfunction.

**Skeletal muscle**

The most common symptom of PM/DM is symmetrical proximal muscle weakness of the extremities. Initially, lower extremity weakness results in difficulty arising from chairs or toilet seats. Upper extremity symptoms follow, with patients experiencing difficulty reaching overhead or combing their hair. Pain or tenderness in the affected muscle sites commonly occurs. Serum muscle enzyme levels (creatine kinase (CK), aldolase, aspartate amino transferase (AST), and lactate dehydrase (LDH) are useful to evaluate the disease activity. The electromyogram findings of myositis include a myopathic pattern of the motor unit action potential, a myopathic recruitment pattern, increased insertional activity, and increased spontaneous activity. The characteristic features of muscle biopsy specimens from PM/DM patients are muscle fiber necrosis with degeneration and regeneration. Lymphocytes are the predominant cells, but other cells including macrophages, plasma cells, neutrophils, basophils, and eosinophils are also infiltrating. Magnetic resonance imaging of the muscle is often useful to identify where inflammation is present and to decide the location of muscle biopsy.

**Skin**

The skin lesion of DM [76] may precede, develop simultaneously with, or follow the onset of myositis. The heliotrope rash, Gottron’s sign, and Gottron’s papules are highly characteristic cutaneous features of DM [23]. The heliotrope rash is a purplish macular erythema/edema located over upper eyelids (Fig. 7.2.6). Gottron’s papules (Fig. 7.2.7) are flat-topped erythematous/violaceous papules over the extensor surfaces of the interphalangeal and/or metacarpophalangeal joints of the hands, elbows, and knees. Gottron’s sign is a
macular erythema that is generally in a distribution similar to Gottron’s papules.

The other skin lesion of DM can be found as symmetrical, macular violaceous erythema overlying the extensor aspect of the fingers, hands, arms, deltoid areas, posterior shoulders and neck (shawl-sign), the V area of the anterior neck (V-sign), the face, the forehead, and the scalp. Photosensitivity, nail fold bleeding, that is punctate bleeding spots observed by naked eyes, periangual erythema, poikiloderma atrrophicans (cutaneous features characterized with a mixture of hyper- and hypopigmentation, atrophy, and telangiectasia), centripetal flagellate erythema consisting of linear streaks on the trunk and proximal extremities, calcinosis cutis (frequent in childhood), and panniculitis can also be seen in patients with DM. Nonpruritic, hyperkeratotic eruption accompanied by scaling, fissuring, and erythema/hyperpigmentation of the palmer and lateral aspects of the fingers (mechanic’s hands) is frequently found in patients with antisynthetase antibodies.

The histopathological findings of the skin from DM patients are characterized with epidermal atrophy, vacuolar alteration of basal keratinocytes, a thickened basement membrane, increased dermal edema and mucin, and a perivascular lymphocytic infiltration of the superficial dermis.

- **Lung**

Lung involvement is common in patients with DM, and may be observed in patients without apparent myositis. This type of pulmonary involvement is frequently seen in patients with antisynthetase antibodies. Interstitial lung diseases may be slowly progressive or even asymptomatic in some patients with DM independent of the existence of antisynthetase antibodies. The most severe lung lesion is rapidly progressive diffuse alveolitis which may be fatal in weeks to months [77]. Antisynthetase antibodies are usually not detected, and an antclinically amyopathic DM (CADM)-140 antibody, a novel antibody associated with clinically amyopathic DM, has been detected in some patients with these progressive alveolitis [78].

- **Gastrointestinal tract**

Involvement of the gastrointestinal tract can be observed but is more common in childhood DM [79]. Swallowing problems (upper dysphasia) are most frequent symptoms, although abdominal discomfort and malabsorption are rarely recognized.

- **Joint**

Polyarthralgias or polyarthritis may occur, especially in patients with overlap syndromes or antisynthetase antibodies, and in childhood DM. The arthropathy associated with antisynthetase antibodies can be chronic and deforming, with interphalangeal thumb joint instability (floppy thumb sign) and erosive, with periarticular calcifications.

- **Peripheral vessels**

Raynaud’s phenomenon can develop in all DM patients except for malignancy-associated subsets. Systemic vasculitis can be observed in childhood DM, but uncommon in adults. The vascular lesions of DM manifest as dermal or subcutaneous nodules, periangual infarcts, and digital ulceration/gangrene.

- **Malignancy and myositis**

The reported incidence of associated malignancy in adult DM varies from 10 to 40%. The overall risk of cancer is greatest in the first 3 years after the diagnosis of myositis, but the cancer can be detected after 3 years. The major risk factors for an associated malignancy appear to be advanced age, presence of skin lesion, and poor response to corticosteroid treatment. By contrast, the presence of interstitial pneumonia, antisynthetase antibodies, or overlap with other connective tissue diseases decreases the likelihood of malignancy. The malignancy precedes the onset of DM in one third of patients, and the cancer is discovered after the development of DM in another third. The remaining third have malignancy at the same time as that of the appearance of their DM. Patients with an associated malignancy have a poor prognosis. Recent studies have reported that autoantibodies reactive with 155 kDa or 140/155 kDa nuclear proteins are associated with malignancy in adult patients with DM [80, 100].

### 7.2.19.3 Autoantibodies

Autoantibodies are often detected in patients with DM/PM, although the role of these antibodies remains unknown. The most representative specific autoantibodies in this group are antisynthetase antibodies [71]. Among antisynthetase antibodies, anti-Jo-1 (histidyl transfer RNA synthetase) antibody is the most common and is found in 20% of patients with classic DM/PM. Interstitial lung diseases, fever, and polyarthritis
7.2 Connective Tissue Diseases

occur more often in patients who have these antibodies (antisynthetase syndrome) as does the mechanic’s hand skin lesion. These patients frequently show recurrence of myositis or interstitial lung diseases. There are some myositis-specific autoantibodies such as anti-single recognition particle (SRP) antibodies and anti-Mi-2 antibodies. Patients with anti-SRP antibodies usually have severe and refractory symptoms. By contrast, patients with anti-Mi-2 antibodies present mild symptoms and good prognosis.

7.2.20 General Therapeutic Outline

Corticosteroids are the only agents approved by the US Food and Drug Administration for DM. However, a number of studies or case reports support the usefulness of other immunosuppressive agents such as methotrexate and cyclosporine in the treatment of myositis. Since DM is a relatively uncommon and heterogeneous disease, there have been few multicenter randomized controlled trials.

At present, the expected mortality in incident cases of PM/DM, excluding those associated with malignancy, is less than 10% at 5 years after initial diagnosis. The significant risk factors excluding malignancy are advanced age, delayed initiation of corticosteroid treatment, pharyngeal dysphasia (aspiration pneumonia), interstitial pneumonia, myocardial involvement, and therapy complications. An acute onset often quickly advanced to a severe grade of involvement, whereas a slower development usually resulted in a milder illness and less severe disability. The serum CK is believed to be the most reliable laboratory indicator of myositis in DM. Although serum aldolase is a less sensitive indicator than CK for active myositis, aldolase levels are occasionally elevated in patients with normal CK level. Another main monitoring tool is muscle strength at the clinical level. Muscle weakness may be the result of myositis, but also of unrecoverable muscle injury.

7.2.21 Current Established Therapies [73]

All patients should receive guidance for the protection from excessive sun exposure including the use of sun-blocking agents. Although topical corticosteroids reduce cutaneous inflammation and pruritus, usually this therapy alone cannot fully suppress the skin eruption.

Systemic corticosteroids remain the initial and primary therapy of DM. Early intervention with systemic corticosteroids has associated with a better prognosis. An adequate initial dose (40–60 mg/day of oral prednisolone) is needed. Most patients require 6–8 weeks of full-dose prednisolone treatment to improve muscle strength, muscle enzyme levels, and skin rash. With improvement, the corticosteroid dosage can be tapered in accordance with the disease activity to a maintenance dose of ~10 mg/day. Pulse intravenous corticosteroids (methylprednisolone 1 g/day for 3 days) may be useful as initial therapy for severe cases.

In patients who failed to respond to corticosteroids or in whom there is a contraindication to the use of corticosteroids, other forms of immunosuppressive agents should be considered. Combination therapy with corticosteroids and methotrexate or cyclosporine A is most often used to treat patients with DM. Azathioprine has also been tried in DM but appears to be less effective. Cyclophosphamide may also be beneficial in refractory cases. Patients with antisynthetase antibodies usually need the immunosuppressive agents such as cyclosporine A or cyclophosphamide in addition to systemic corticosteroid therapy because of refractory myositis or interstitial lung disease. Intravenous immunoglobulin is an effective short-term treatment for refractory DM with the advantage of low toxicity [81], although its long-term effect remains unknown.

Calcium deposits in the skin that occur most commonly in the childhood subset have been intractable, although calcium channel blockers and warfarin are often used [82, 83]. The surgical removal can be considered if the calcium deposits are symptomatic or disturb the physical function.

7.2.22 Experimental Approaches

New immunosuppressant options such as tacrolimus and mycophenolate mofetil have been tried in myositis or interstitial lung disorders in PM/DM or antisynthetase syndrome. A retrospective study and case reports have demonstrated that tacrolimus was useful for refractory myositis or antisynthetase syndrome [84]. Mycophenolate mofetil has been reported to be effective in myositis patients who were resistant to conventional immunosuppressive agents [85].
In addition to rheumatoid arthritis and SLE, some autoimmune disorders including DM have now been investigated for the efficacy of B cell-targeted therapy. Several open studies or case reports have demonstrated that B cell depleting therapy using anti-CD20 monoclonal antibody (rituximab) is effective in myositis patients who were resistant to conventional immunosuppressive agents [86].

7.2.23 Complications to Avoid

Screening for underlying malignancy must be performed in all adult patients with DM. Gastrointestinal hemorrhage in children secondary to vasculitis is often fatal.

Take Home Message

- DM is a disease consisting of heterogeneous subsets. Most patients, especially patients with antisynthetase antibodies, need some immunosuppressant agents in addition to corticosteroid. Anti-B cell depletion therapy using rituximab may be a promising therapy for refractory DM.

7.2.24 Global Variations

There is little global variation in treatment.

7.2.25 Polyarteritis Nodosa

Key Features

- Systemic vasculitic disease that predominantly involves medium-sized artery
- Skin manifestations such as subcutaneous nodule, livedo, and skin ulcer
- Peripheral neuropathy is common
- Renal involvement such as renal insufficiency and hypertension
- Gut involvement such as small colon infarction
- Biopsy or angiography is useful for diagnosis
- Microscopic polyangiitis
- Systemic vasculitic disease that predominantly involves small vessels
- Antineutrophil cytoplasmic antibodies (ANCA), especially antibodies against the myeloperoxidase (MPO-ANCA) are positive
- Cutaneous manifestation such as palpable purpura and livedo
- Rapid progressive glomerulonephritis is a characteristic renal involvement
- Alveolar hemorrhage can be found

7.2.26 Etiology and Pathophysiology

Classic polyarteritis nodosa (PN) and microscopic polyangiitis (MPA) are collagen diseases that show ischemic and inflammatory organ injuries and constitutional symptoms such as fever and body weight loss [23, 87, 88]. These symptoms are derived from necrotizing vasculitis of small and medium-sized arteries. Although the pathogenesis of these vasculitic diseases remains unclear, the development has been considered to depend on genetic and environmental factors.

Infections, drugs, and exposures to other antigens have been suggested as triggers for the development of vasculitis. Previous findings suggest that immune complexes including some antigens such as hepatitis B activate leukocytes and endothelial cells leading to final common pathway of inflammation and ischemia in PN. On the other hand, a direct role of myeloperoxidase (MPO) – ANCA for the development of glomerulonephritis and vasculitis has been demonstrated in a mouse model of MPA [89].

During the process of vasculitis, activated endothelial cells can stimulate the inflammation by producing proinflammatory cytokines. Among them, IL-1β and TNF-α increase the expression of adhesion molecules (selectins, integrins, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1) at endothelial...
cells, leading to the inflammatory cell infiltration into the targeted organ tissues. IL-8 made by activated endothelial cells attracts leukocytes to the vascular wall. A high concentration of nitric oxide produced by proinflammatory cytokines and superoxide anion released by activated neutrophils may cooperatively contribute to vascular injuries.

7.2.27 Clinical Characteristics and Diagnosis

7.2.27.1 Epidemiology

The overall average incidence of PN-type systemic vasculitis has been estimated to range between 9 and 77 cases per million population per year. These estimates included PN, MPA, connective tissue disease-associated polyarteritis and Churg-Strauss syndrome. PN or MPA is more common in males rather than females. The onset of PN or MPA is observed in any age, but the mean age is about 50 years.

7.2.27.2 Classification

In 1993, Chapel Hill International Consensus Conference on vasculitis nomenclature proposed standard definitions for 10 distinct vasculitis entities and grouped them into three familiar groups, based on the size of involved arterioles [90]. From this consensus, MPA was distinguished from PN by small vessel (arterioles, venules or capillaries) involvement with no immune deposits. By contrast, PN was defined as necrotizing vasculitis of small and medium-sized muscle arteries without small vessel involvement. However, it is generally accepted that PN can also involve the small vessels, suggesting that even this criterion remains imperfect. Hepatitis B infection or angiographic finding of aneurysms can be seen in patients with PN. By contrast, the involvement of rapidly progressive glomerulonephritides or alveolar hemorrhage strongly suggests the existence of MPA rather than PN. MPO-ANCA is detected in sera from 60% of patients with MPA. ANCA-positive patients with systemic vasculitis lacking specific features of other ANCA-associated vasculitis such as Wegener’s granulomatosis or Churg-Strauss syndrome are generally considered as having MPA. Other differential diagnosis of PN or MPA includes infection, drug, connective tissue disease or malignancy-associated vasculitis.

7.2.27.3 Clinical Features

The patients with systemic vasculitis usually show general symptoms such as fever, malaise, and body weight loss. Additionally, patients may develop ischemic and/or inflammatory manifestations of vasculitis in any organs including skin, muscles, joints, nerves, lungs, and kidneys.

Fig. 7.2.8 Livedo developed on lower leg of a woman with polyarteritis nodosa
• **PN**

Cutaneous features are found in 25–60% of patients with PN. These include subcutaneous nodule, livedo, palpable purpura, ulcer, and gangrene (Fig. 7.2.8). Cutaneous PN, a necrotizing vasculitis restricted to the skin shows skin lesion similar to that of PN. Although general symptoms including fever, arthralgias, myalgias and peripheral neuropathy may be found in patients with cutaneous PN, internal organ involvement is not detected in these patients. However, a part of cutaneous PN may shift to systemic PN during the clinical course.

Hypertension or abnormal renal function derived from renal involvement is found in about half of PN patients. Gastrointestinal manifestations include nausea, vomiting, abdominal pain, hemorrhage, perforation, and infarcts caused by vasculitis of the upper or lower gastrointestinal tract. The development of microaneurysms in the mesenteric, hepatic, or renal arteries is characteristic. Arthralgia, arthritis, and ischemic myalgias are frequently present in patients with PN. Peripheral neuropathy is common and sometimes is the initial manifestation. Involvement of the central nervous system seen in some of the patients is a life-threatening event. Otherwise, ischemic heart diseases, interstitial pneumonia, testicular pain/epididymitis or ocular involvement can be found.

Most laboratory tests are nonspecific and reflect the systemic inflammatory nature of PN. Elevated acute-phase reactants, anemia due to inflammation, and thrombocytosis are frequently detected in patients with active PN. Hepatitis B surface antigen is found in 7–54% of patients. ANCA is usually negative in serum. The histopathology consists of focal, necrotizing vasculitis of predominantly middle-sized arteries characterized by fibrinoid necrosis and pleomorphic cellular infiltration with nuclear dust. If biopsy specimen cannot be obtained from accessible involved tissues such as skin and nerve, complete abdominal angiography to evaluate the medium-sized vessels may be useful for diagnosis or information on prognosis.

• **MPA**

MPA is a multi-system disease caused by pauci-immune small vessel vasculitis, which are closely associated with the presence of ANCA. ANCAs are autoantibodies directed against the neutrophil granule enzymes including MPO (pANCA) and proteinase 3 (cANCA) and may play a direct role in the pathogenesis of disease. These ANCA-associated vasculitis are characterized by focal necrotizing inflammation of small arteries, arterioles and veins.

Skin is more commonly involved in MPA than in PN. Palpable purpura is the most common skin manifestation, although livedo, splinter hemorrhages or ulceration can be found (Fig. 7.2.9). Crescentic necrotizing, and sometimes rapidly progressive, glomerulonephritis is the major feature of MPA. Pulmonary involvement is also a representative clinical feature and includes dyspnea, pleural effusion, alveolar hemorrhage, and interstitial pneumonia. Peripheral neuropathy with symmetric mixed motor and sensory components, or mononeuritis multiplex pattern can be seen in most patients. MPA as well as PN may cause ischemia in the heart and gastrointestinal tract.

The biopsy of lesional skin or involved peripheral nerves is useful for diagnosis. In patients suspected for glomerulonephritis, renal biopsies usually provide the
important information for diagnosis and prognosis. The renal biopsy tissue in MPA shows segmental necrosis and crescent formation, together with little or no endocapillary proliferation. Little or no immunodeposits by immunofluorescent staining and electron microscopy is characteristic and called as pauci-immune glomerulonephritis. The presence of MPO-ANCA supports the clinical diagnosis, although this is not specific for this disease.

7.2.28 General Therapeutic Outline

In PN or MPA, the prognosis is dependent on the involvement of visceral organs. The prognosis of untreated PN-type systemic vasculitis had been poor, but survival has improved with the use of corticosteroids. Furthermore, the use of the combination of cyclophosphamide and corticosteroids has significantly improved the prognosis in patients with severe organ involvement [91, 92]. Thus, recent studies have demonstrated that a 5-year survival rate has increased to 50–80%.

During the follow-up of PN or MPA, the general clinical status, organ involvement, and inflammatory marker should be monitored. The titer of MPO-ANCA may associate with the disease activity or severity in some MPA patients. Relapses are very common and most patients need treatment during their life.

7.2.29 Current Established Therapies

Corticosteroids in high doses (40–60 mg/day), sometimes pulse steroids therapy (intravenous methylprednisolone 1 g×3 days), remain the initial mainstay of therapy for both PN and MPA. To maintain the remission, patients usually need a low dose of corticosteroids for long time. Corticosteroids alone may be sufficient for patients who do not have severe organ involvement. The combination of corticosteroids and immunosuppressive agents such as cyclophosphamide is clearly effective in inducing clinical remission in patients with severe organ involvement in the kidneys, lungs, nerves, heart, and gastrointestinal tract.

It has been reported that the efficacy of pulse intravenous cyclophosphamide (every 2 weeks) and daily oral cyclophosphamide is comparable when the agent is used with daily oral corticosteroids [93]. However, infectious complication was more frequent in oral cyclophosphamide group in that study. A randomized controlled study in Europe demonstrated that no significant difference was found between cyclophosphamide and methotrexate for induction of remission in early systemic ANCA-associated vasculitis [94]. A randomized controlled trial for ANCA-associated vasculitis for maintenance therapy in Europe demonstrated that oral azathioprine was as effective as cyclophosphamide [95]. That is, the withdrawal of cyclophosphamide and the substitution of azathioprine after remission did not increase the rate of relapse.

7.2.30 Experimental Approaches

Current trials are investigating mycophenolate mofetil, an inhibitor of the proliferation of T and B lymphocytes, as an alternative to other immunosuppressant agents. A randomized controlled study in Europe reported that a single course of intravenous immunoglobulin reduced disease activity in persistent ANCA-associated systemic vasculitis, but this effect was not maintained beyond 3 months [96]. Although a retrospective study suggests that autologous hematopoetic stem-cell transplantation is effective for systemic vasculitic diseases [97], its evaluation remains to be tested in prospective controlled studies. A randomized controlled study in United States clarified that targeting TNF-α therapy was not effective for the maintenance of remission in patients with Wegener’s granulomatosis, one of ANCA-associated systemic vasculitis [98]. Recent open studies or case reports demonstrated that B cell depletion using rituximab (antihuman CD20 Ab) are effective with low toxicity for ANCA-associated vasculitis. Although relapse was commonly found after withdrawal, re-treatment was rapidly effective [19].

7.2.31 Complications to Avoid

Complications of treatment, such as opportunistic or severe infection are frequently found in patients being treated with high-dose corticosteroids and/or immunosuppressive agents such as cyclophosphamide. Thrombosis secondary to vasculitic events should be avoided.
Take Home Message

› Corticosteroids alone or in combination with cyclophosphamide are the most popular treatment for PN or MPA. Early induction of remission and avoidance of therapy complication are critical for the prognosis.

7.2.32 Global Variations

There is little global variation in treatment.

References

7.3.1 Etiology and Pathophysiology

The etiology of the vasculitic process is only partially understood, which in part is due to the relative rarity of this disease and the diversity of the pathophysiological processes that can attack the vascular wall. It may involve processes secondary to infections leading to vascular occlusion and pathogenic effects of infectious agents; it may also involve various immunologic mechanisms that drive autoimmune disease as diverse as drug reactions, rheumatic disorders, inflammatory bowel disease, and malignant diseases. Vasculitis is therefore also dealt with as part of the skin manifestations of rheumatic disorders (Chap. 5.7), connective tissue diseases (Chap. 7.2), and noninfectious granulomatous diseases (Chap. 7.6).

Pathophysiology may partly reflect the classic mechanisms of Type II, III, and IV reactions as described by Coombs and Gell [1]. Traditionally, vasculitis is considered to be an immune complex-mediated process as in allergic vasculitis, Schönlein-Henoch Purpura, mixed cryoglobulinemia, and presumably T-cell mediated diseases e.g., Churg-Strauss-Syndrome. In most patients, a combination of these reactions is more common. Here, a number of factors and inflammatory pathways interact including autoantibodies and immune complexes, inflammatory cells (being antigen specific or cells belonging to the innate immune system as e.g., neutrophilic granulocytes), complement, adhesion molecules, cytokines (IL-1, TNF-α) and growth factors, the fibrinolytic system as well as topical blood flow regulation [2–4].

Involvement of the innate immune system in diseases such as Behçet’s disease and pyoderma gangraenosum has recently been suggested [5, 6]. There appears to be a certain genetic predisposition with a lack of complement (e.g., hypocomplementemic urticarial vasculitis) and other to date unidentified markers. However, in comparison to other inflammatory diseases e.g., rheumatoid arthritis or SLE, there are only scarce reports on the role of particular genetic risk factors.

The different weight of these pathophysiological factors in the different forms of vasculitis affecting small or large vessels should result in different treatment approaches. Thus, therapy of vasculitic processes encompasses a wide range of substances including the use of corticosteroids, immunosuppressive agents, interferons, biologics (e.g., anti-TNF-α agents) as well as anticoagulants.

7.3.2 Clinical Characteristics and Diagnosis

Numerous classifications of cutaneous vasculitis exist: (1) clinical (here differences may occur from subspecialty to subspecialty e.g., dermatologists
vs. rheumatologists), (2) histopathological, and (3) pathophysiological. As far as therapy is concerned, the pathophysiological classification is most important. However, for a comprehensive, interdisciplinary therapeutic approach, knowledge of the major aspects of these classifications is essential [7–9].

For the clinician-dermatologist, the most practical classification is shown in Table 7.3.1, which must also consider whether the patient suffers from pure cutaneous vasculitis or cutaneous vasculitis with internal organ involvement.

For the rheumatologist, the Chapel Hill classification [10] is widely used and distinguishes between vasculitis of large vessels e.g., temporal arteritis (giant cell arteritis), vasculitis of medium sized vessels e.g., periarteritis nodosa, and vasculitis of small vessels e.g., leucocytoclastic vasculitis, microscopic polyangiitis. Overlap involvement of small and medium sized vessels as well as large and medium sized vessels may occur and has led to simplified schemes discerning only between large and small vessel diseases. For details on the treatment of these diseases, please refer to Chaps. 5.6, 5.7, 7.2, 7.3, and 7.6.

Important aspects of the history and the clinical examination are localization, extent and severity of the vasculitic skin lesions or palpable purpura (see Fig. 7.3.1), and depending on the organ system involved, the presence of blood in urine, stool, nasal discharge, presence of hemoptysis or dyspnea, abdominal pain, arthralgia or arthritis and signs of nervous system involvement.

Laboratory investigation should also aim to investigate the general inflammatory component of the disease as well as the organ system involved by performing ESR, WBC, creatinine, urine analysis, creatinine clearance and protein excretion in 24 h, and search for occult blood in stool. A skin biopsy is mandatory, including immunofluorescence in particular when Schönlein–Henoch Purpura is suspected. The extent of serologic testing may vary from center to center and includes the determination of antinuclear antibodies (ANA), complement C3, C4, antineutrophil cytoplasmic antibodies (ANCA), rheumatoid factor,
cryoglobulins, antiphospholipid antibodies, hepatitis B, C titers. For the dermatohistopathologist the diagnosis of vasculitis requires necrosis of the vessel wall with deposition of fibrinoid material. Leucocytoclasis, extravasation of erythrocytes, endothelial cell swelling, luminal thrombosis and edema may accompany this process. Interestingly, purpura may not always be associated with cutaneous vasculitis, when biopsied, a typical example being pigmented purpuric dermatosis. Histopathologic differential diagnosis of the vasculitic process is based on analysis of the type of vessel involved (small, medium-sized, large), composition of the inflammatory infiltrate, and associated findings [11]. Diagnosis may be hampered by the stage of the disease, level of activity, and the type of treatment, which may all modify the histopathological findings. Thus, it is of utmost importance to receive a biopsy from a fresh, untreated lesion with sufficient size and depth. A vasculitis of medium sized arteries in the subcutaneous tissue may be diagnosed only when a reasonable amount of tissue is available and sometimes repeated biopsies will become necessary to reach a definite diagnosis.

A number of diseases affecting the vascular bed can mimic vasculitis such as calciphylaxis, cholesterol emboli, Degos disease, thrombangiitis obliterans, and heparine necrosis and should be considered in the differential diagnosis (see Table 7.3.2). Treatment with corticosteroids and immunosuppressive agents in these diseases is not indicated.

### Table 7.3.2 Mimickers of cutaneous vasculitis

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol emboli</td>
</tr>
<tr>
<td>Calciphylaxis</td>
</tr>
<tr>
<td>Degos disease</td>
</tr>
<tr>
<td>Thrombangiitis obliterans</td>
</tr>
<tr>
<td>Heparine necrosis</td>
</tr>
<tr>
<td>Cumarine necrosis</td>
</tr>
</tbody>
</table>

7.3.3 General Therapeutic Outline

In a number of case series it has been shown that in about 50% of cases small vessel vasculitis remains limited to the skin without identifiable extracutaneous involvement. Furthermore the majority of cases are episodic and self limited with about 10% of patients developing recurrent or chronic involvement. Despite chronic or relapsing disease most patients carry a good overall prognosis [12, 13].

The evidence level for the therapy of cutaneous vasculitis is low. There is a complete lack of double-blind controlled studies for treating cutaneous vasculitis. Therapeutic recommendations are therefore in general based on personal experience, reports in the literature on small case series, and experience from autoimmune diseases, where a better evidence level has been obtained e.g., rheumatoid arthritis, SLE.

7.3.4 Current Established Therapy

Patients with small vessel vasculitis may be managed by different specialists apart from dermatologists, including rheumatologists, nephrologists and pulmonologists depending on the dominant organ system involved. The dermatologist may also serve as primary care provider guiding diagnosis and therapy.

To date, few controlled studies regarding treatment of cutaneous vasculitis have been conducted. Case reports and small case series exist, for instance, on the use of dapsone, colchizine and pentoxyfilline. No controlled study as to the efficacy of prednisone or other immunosuppressives is available.

It is recommended to design therapy according to three major determinants: (1) severity of skin involvement; (2) severity of internal organ involvement; and (3) rate of change. Therapy should not be delayed whilst awaiting data for a definite diagnosis. Systemic vasculitis requires prompt initiation of therapy (Table 7.3.3).

Bacterial, rickettsial, viral, and fungal infections should be excluded by appropriate investigations.

The most common origin of vasculitis is idiopathic (ca. 50% in a number of case series) followed by drug reactions and specific forms of vasculitis. Therefore a detailed drug history is mandatory. Prominent drugs that may induce a vasculitis are allopurinol, antibiotics, β-blockers, glibenclamide etc. (for a detailed review see e.g., [14]). Temporal correlation is essential, as reactions starting more than 10–14 days after the last intake are unlikely to be related to the suspected drug. The length of time for treatment must be individualized.
In mild forms, mainly involving the lower extremities, with no visible necrosis, compression stockings may help to reduce hydrostatic pressure on the vessel wall of the lower extremities. In mild forms of cutaneous vasculitis, topical therapy with high potency class III or IV corticosteroids may suffice.

In more severe cases with significant cutaneous ulceration and significant systemic manifestations, a short course of oral corticosteroids (3–6 weeks) starting with 0.5–1 mg/kg/day may become necessary to protect internal organs (e.g., kidney) and minimize progression of skin involvement.

Rebound flare may pose a problem with rapid reduction of dose, therefore in uncomplicated cases corticosteroids should be tapered slowly over 4–6 weeks. For longer treatment periods with corticosteroids, the risk of serious side effects e.g., arterial hypertension, diabetes mellitus, osteonecrosis of the hip increases. Therefore, when classic vasculitic diseases are diagnosed (see Chaps. 5.6, 5.7, 7.2, 7.3, and 7.6), immunosuppressive agents should be instituted early in the disease process, as it usually takes 4–8 weeks until classic immunosuppressive drugs e.g., azathioprine develop their full therapeutic effect. The treatment plan should then take into account concurrent chronic diseases of the patient i.e., diabetes mellitus, heart disease, underlying malignancies, and infections, which may interfere with the immunosuppressive regimen.

To achieve steroid sparing immunosuppressive agents such as azathioprine, MTX or MMF are recommended (see Table 7.3.2) [15]. When azathioprine is used it is recommended that thiopurine methyltransferase (TPMT) activity be determined. Decreased activity of TPMT is responsible for severe myelotoxic side effects, whereas increased TPMT activity may decrease the efficacy of azathioprine.

Maintenance therapy should be continued for at least 6–8 weeks after the skin lesions have cleared. This will vary from patient to patient determined by the severity of the disease, concomitant illnesses, the ability of the patient and physician to maintain close contact, and the attitude of the patient.

### 7.3.5 Experimental Approaches

Treatment of autoimmune disorders is still difficult since long-term administration of corticosteroids, mostly in combination with cytotoxic drugs, are the mainstay of therapy. Side-effects either related to the nonspecific action on the immune system or systemic pathogenic effects often limit their application (Table 7.3.2).

High-dose intravenous immunoglobulins are used to treat a wide range of inflammatory diseases and a small number of reports exist on the successful use of 2 g/kg (split over 3–5 days) monthly for varying intervals [16–19]. Similarly, in particular when immune complex associated pathogenesis is suspected plasmapheresis or immune apheresis may be considered [20–24].

With the advent of biotechnology, new therapeutic tools have emerged targeting specific molecules involved in tissue inflammation. Two approaches targeting B-cells a part of the adaptive immune system and TNF-α have recently shown promising results in vasculitic diseases and shall be shortly discussed.

B-lymphocytes are critical for the regulation of immune responses and production of antibodies. They also function as antigen-presenting cells and are involved in the regulation of the differentiation and activation of T-lymphocytes and dendritic cells. Rituximab is chimeric monoclonal antibody directed against CD20 a pan B cell glycoprotein that is expressed on pre-B cells, immature B cells, naïve and memory B cells, but not on plasma cells.

Rituximab has been used to treat various refractory autoimmune diseases [25, 26]. Idiopathic thrombocytopenic purpura (ITP) was the first autoimmune disorder that was successfully treated and there is also clear evidence of efficacy in autoimmune haemolytic anemia. Subsequently, rituximab has been applied in rheumatoid arthritis, systemic lupus erythematosus, myasthenia

---

**Table 7.3.3 Overview on therapy of cutaneous vasculitis**

<table>
<thead>
<tr>
<th>Mild skin disease (purpura)</th>
<th>Stockings, Topical class III/IV corticosteroids, Systemic low dose steroids (&lt;0.5 mg/die)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe skin disease (ulcers, hemorrhagic necroses)</td>
<td>Syst. steroids (0.5–1.0 mg/kg/day), Addition of: Azathioprine (1–2 mg/kg/die) or Mycophenolate mofetil (2 g/day) or MTX (10–25 mg/week)</td>
</tr>
<tr>
<td>Recalcitrant severe skin disease</td>
<td>Intravenous immunoglobulin (2 g/kg), Plasmapheresis, immune adsorption, TNF-inhibitors, anti-CD20 therapy (Rituximab)</td>
</tr>
</tbody>
</table>
7.3 Cutaneous Vasculitis

gravis, Wegener’s granulomatosis, Sjögren syndrome, and dermatomyositis among others [27–30]. Long-term remissions without further therapy have been observed in patients with these disorders suggesting that immune tolerance to autoantigens may be re-established.

TNF-α is considered as a key cytokine of inflammatory processes and its blockade has been very successful in controlling immune-mediated disorders such as rheumatoid arthritis and psoriasis. Two recombinant approaches were chosen to achieve this end: (1) a soluble receptor, (2) chimeric or humanized antibody targeting TNF-α [31–33]. Therefore it is not surprising that a number of case reports and clinical studies describe the partially successful use of this concept in vasculitic diseases such as Wegeners granulomatosis and Behcets disease, which may present with cutaneous vasculitis [34–38]. In this context it is of interest that infliximab was recently approved in Japan for the treatment of “Behcet’s disease complicated with refractory uveoretinitis which does not respond to conventional therapies” [36]. However, it has to be kept in mind that TNF-α inhibitors themselves appear to have the potential to induce vasculitis [39, 40].

**Take Home Message**

Vasculitis presents with a wide range of clinical manifestations. For the dermatologist who is usually confronted with skin involvement, it is pivotal to exclude and be aware of internal organ involvement. Also, vasculitis may be secondary to a wide range of conditions, making the prompt recognition and treatment of associated disorders essential for appropriate patient management. Therapy should then be guided by the pathophysiological process identified and the extent of the clinical manifestation.

### 7.3.6 Global Variations

In some countries, the dermatologist may serve a role similar to the primary care provider, coordinating the different subspecialties involved in care of the patient. Multispecialty vasculitis clinics that provide interdisciplinary care are rare.

Depending on the financial capabilities of the respective health care system, the time point of initiation of corticosteroid therapy and associated immunosuppression as well as the extent of expensive experimental approaches e.g., the use of biologics may vary.

**References**

7.4.1 Etiology and Pathophysiology

7.4.1.1 Acute GVHD (aGVHD)

On the basis of the original description of GVHD by Billingham in 1966, the classical necessary conditions that lead to GVHD presentation are three: (1) Administration of immunocompetent cells, (2) histoincompatibility between donor and recipient, and (3) inability of the recipient to destroy or inactivate the transfused or transplanted cells. The development of aGVHD under these conditions is divided into three phases [1, 2].

(a) Conditioning regimen
The tissue damage (most apparent in gut) leads to hyperexpression of adhesion molecules and HLA antigens on host cells.

(b) Donor T-cell activation
Infused T-cells from the graft are activated by the recognition of host antigens presented by antigen-presenting cells. Activation of T-lymphocytes is followed by a “cytokine storm” – production and secretion of multiple pro-inflammatory cytokines.
Both humoral (cytokines) and cellular (e.g., NK cells, cytotoxic T-lymphocytes, macrophages) effector mechanisms lead to apoptosis in target organs and tissue damage.

### 7.4.1.2 Chronic GVHD (cGVHD)

The pathophysiology of cGVHD is at present still poorly understood. Similar mechanisms as in aGVHD have been proposed with the emphasis on thymic damage in the effector phase of aGVHD (see Sect. 4.1.1). The distorted thymic function in theory leads to aberrant “thymic T-lymphocyte” education. Autoreactive T-lymphocytes escape the negative selection in the thymus and are responsible for “autoimmune-like” phenomena frequently associated with cGVHD.

Other mechanisms currently under investigation are the following: distorted Th1/Th2 ratio, the number of regulatory T cells present, B-cell subpopulation distribution, and others [3, 4].

### 7.4.2 Clinical Characteristics: Diagnosis and Grading

#### 7.4.2.1 aGVHD

#### 7.4.2.1.1 Clinical Characteristics

Skin involvement together with cholestatic hepatopathy (increase of alkaline phosphatase and gamma glutamyl transpeptidase usually more marked than that of the transaminases) and gastrointestinal involvement (diarrhea of varying degrees of severity, anorexia, vomiting) is typical. aGVHD can present with a maculopapular rash, which is usually present on palms, soles, and ears but can be generalized. Without appropriate therapy, it can evolve into erythroderma and extremely painful bullous exfoliation.

#### 7.4.2.2 cGVHD

#### 7.4.2.2.1 Clinical Characteristics

The clinical presentation of cGVHD on the skin and other organs is highly variable and can be divided into lichenoid and sclerodermatous types whereby the lichenoid can progress into the sclerodermatous type in the course of time; the sclerodermatous form can

---

**Table 7.4.1 Classification of GVHD**

<table>
<thead>
<tr>
<th>Category</th>
<th>Time of symptoms after HCT or DLI</th>
<th>Presence of acute GVHD features</th>
<th>Presence of chronic GVHD features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute GVHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic acute GVHD</td>
<td>≤100 days</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Persistent, recurrent or late onset aGVHD</td>
<td>&gt;100 days</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic chronic GVHD</td>
<td>No time limit</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Overlap syndrome</td>
<td>No time limit</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

According to [7]
develop without a preceding lichenoid stage as well (Fig. 7.4.1) [5, 6].

7.4.2.2.2 Diagnosis

As suggested in the NIH Consensus Development Project [7], diagnosis of cGVHD can be confirmed by the presence of at least one “diagnostic sign.” If only “distinctive” or even less specific signs are present, the pertinent biopsy is recommended. Dermatological “diagnostic signs” are the following: poikiloderma, lichen planus-like features, sclerotic features, and lichen sclerosus-like features. The following signs are “diagnostic” for the oral cavity: lichen-type features, hyperkeratotic plaques, and restriction of the mouth opening due to sclerosis.

7.4.2.2.3 Grading of cGVHD

Since the traditional grading system [8] – which discriminates between limited and extensive form of cGVHD – does not stratify patients for outcome [9], a new system has recently been proposed [7]. This system remains yet to be validated in clinical practice. A score ranging from 0 to 3 is given to every involved organ; a score of 3 indicating the most severe impairment. For the skin the scoring is as follows (Table 7.4.3):

Another possibility to evaluate skin changes in cGVHD is to use a validated skin scoring system, which was recently developed [10].

7.4.3 General Therapeutic Outline

7.4.3.1 aGVHD

As first line therapy of aGVHD, standard guidelines with small variations are usually followed by most established specialized centers. The approach to the therapy of aGVHD starts with the choice of prophylaxis and/or T-cell depletion.
Systemic therapy of established aGVHD must be provided by an experienced physician. The individualized and careful decision making process must always take into account that the risks of “over” treatment may lead to an increased risk of relapse of the underlying malignancy, to infections and additional complications. Systemic steroids are the mainstay of therapy (see Sect. 4.1.3).

### 7.4.3.2 cGVHD

The necessity of an individualized approach to the treatment of cGVHD is of equal importance. Standard topical therapies are applied for mild cases. The NIH Consensus Development Project recommends considering the use of systemic immunosuppressive therapy for patients with involvement of three or more organs or with a score of 2 or more in any single organ.

### 7.4.4 Current Established Prophylactic and Therapeutic Modalities

#### 7.4.4.1 aGVHD

##### 7.4.4.1.1 T-Cell Depletion

Currently, this method is considered the most effective for GVHD prevention [11]. There are several approaches to deplete T-lymphocyte from the graft. Technically this can be done either in vitro (currently rarely done) or in vivo (e.g., addition of antithymocyte globulin or other agents such as antiCD-52 antibody to the conditioning regimen). Achieving a decreased rate of aGVHD can unfortunately be associated with an increased risk of relapse [12], risk of graft failure [11], and profound immunosuppression with an increased rate of infections or a higher rate of EBV associated lymphoproliferative disease [13]. The approaches to T-cell depletion differ among transplant centers.

#### 7.4.4.1.2 Posttransplant Prophylaxis

GVHD prophylaxis is an integral part of every conditioning regimen given before allogeneic stem cell transplantation. The “gold standard” regimen is a combination of short term methotrexate and intravenous Cyclosporin A [14]. In the setting of myeloablative transplants the duration of prophylaxis is 6 months, in the case of reduced intensity conditioning it is often tapered earlier. Other combinations of immunosuppressive drugs are used as well [15, 16].

#### 7.4.4.1.3 First-Line Therapy of Established aGVHD

The “watch and wait” approach is currently an accepted approach for grade I skin aGVHD [17]. If the patient is symptomatic, then topical steroids may be used but systemic steroid therapy should not be instituted (in the effort to use the possible graft-versus-tumor effect [18]). Established first line therapy is corticosteroids in the form of Methylprednisolone at a dose of 2 mg/kg/day in association with cyclosporine A [19]. Patients responding to this therapy have a significantly better prognosis than nonresponders.

### Table 7.4.3 Scoring of skin symptoms of cGVHD

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td>&lt;18% Body surface area (BSA) with disease signs but no sclerotic features</td>
<td>19–50% BSA or involvement with superficial sclerotic features “not hidebound” (able to pinch)</td>
<td>&gt;50% BSA or deep sclerotic features – “hidebound skin” (unable to pinch) or impaired mobility, ulceration or severe pruritus</td>
<td></td>
</tr>
</tbody>
</table>

According to [7]
### 7.4.4.2 cGVHD

#### 7.4.4.2.1 T-Cell Depletion

T-cell depletion by use of thymoglobulin (ATG) has been shown to prevent cGVHD development [20]. Its use must be evaluated thoroughly as it can be associated with a significant increase in risk for relapse [12], (see also Sect. 4.1.2).

#### 7.4.4.2.2 First-Line Therapy for cGVHD

The current standard first-line therapy for cGVHD is prednisolon in a dose of 1 mg/kg in one daily dose [7]; this dosage should not be reduced until the first signs of improvement appear. The taper should be interrupted at a dose of 1 mg/kg on an alternate day schedule until all the (reversible) manifestations of cGVHD are cleared. Addition of cyclosporine A (with target levels of CSA 150–300 mg/mL) to the first-line therapy is possible and can help reduce the risk of steroid-related toxicity [21]. Tacrolimus can be added as an alternative (Table 7.4.4).

If recurrence occurs under prednisolon taper, the dose should be increased by two steps and treatment should last for at least 3 months till the next attempt of taper is tried. Prednisolon should be discontinued as the first drug in the combination; cyclosporine A can be reduced further on in the treatment.

#### Table 7.4.4 Prednisolon taper scheme

<table>
<thead>
<tr>
<th>Week</th>
<th>Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1/0.5</td>
</tr>
<tr>
<td>4</td>
<td>1/0.25</td>
</tr>
<tr>
<td>6</td>
<td>0.7 q.o.d.</td>
</tr>
<tr>
<td>8</td>
<td>0.55 q.o.d.</td>
</tr>
<tr>
<td>10</td>
<td>0.45 q.o.d.</td>
</tr>
<tr>
<td>12</td>
<td>0.35 q.o.d.</td>
</tr>
<tr>
<td>14</td>
<td>0.25 q.o.d.</td>
</tr>
<tr>
<td>16</td>
<td>0.20 q.o.d.</td>
</tr>
<tr>
<td>18</td>
<td>0.15 q.o.d.</td>
</tr>
</tbody>
</table>

According to [19]

### 7.4.5 Second-Line Therapies and Experimental Approaches

#### 7.4.5.1 Experimental Approaches to Prophylaxis

Recently experimental cellular therapies (extracorporeal chemotherapy (photopheresis, extracorporeal photoinmunotherapy, ECP), antigen-presenting cells downregulation) to prevent aGVHD have been explored [22].

#### 7.4.5.2 Second-Line Therapies and Experimental Approaches to Therapy

Steroid refractory aGVHD is a poor prognostic factor and places the patient at a high risk of premature death. Therapy – refractory cGVHD leads to severely diminished quality of life and long-term immunosuppression with high risk of infectious complications. At present, no second-line or third-line therapies for refractory acute or cGVHD can be called standard. Various therapeutic modalities used in this indication are listed [22–43], the ones in “bold” with short comments (see Sects. 5.2.1 and 5.2.2) are those that appear most promising in the future based on the authors’ experience and current available evidence (limited mostly to small retrospective studies). In addition to considerations of efficacy, organ toxicity, increased risk of infection and ability to spare long-term steroid use must be taken into account when choosing the appropriate treatment strategy.

#### 7.4.5.2.1 Strategies for Steroid-Refractory aGVHD

**Monoclonal antibodies:**

*Etanercept – antiTNF* – etanercept has been used in a number of studies alone or in combination (with steroids, ATG, daclizumab, mycophenolate mofetil). Currently, it is also under investigation in the first line treatment setting in combination with steroids. Preliminary data appears promising but further confirmatory studies are needed [32, 36, 43].
**Daclizumab – antiIL-2R** – very promising results (complete resolution in 68.8%) of phase II studies mainly in pediatric patients and patients with gut and skin involvement (lower efficacy in liver aGVHD) were observed. In one long-term follow-up study the results are worse due to the high rate of infectious complications and infection-related deaths. A comprehensive antimicrobial prophylaxis is recommended [25, 40].

- Inolimomab – antiIL-2R
- Infliximab – antiTNF
- Alemtuzumab – antiCD52
- Abx-cbl – antiCD147
- Visilisumab – antiCD3

**Extracorporeal photopheresis (ECP)** – in a phase II study, patients with aGVHD II-IV achieved a high response rate (complete response 82% for skin, 61% for gut and 61% for liver involvement). Patients with a complete response had over 50% long-term survival [33].

**Mesenchymal stem cells** – in vitro data has shown that mesenchymal cells inhibit the formation of cytotoxic T-cells and NK-cells. In pilot studies patients with steroid refractory aGVHD grade III-IV responded with high overall response rates (69%) after mesenchymal cells infusion (from HLA identical siblings, haploidentical or even unrelated donors) [44, 45].

- Antithymocyte globulin (ATG)
- Sirolimus
- Mycophenolate mofetil
- Pentostatin
- Thalidomide
- Suicide gene transduction of T cells
- High-dose or intra-arterial steroids
- Pulse cyclophosphamide
- Denileukin diftitox
- PUVA

### 7.4.5.2.2 Strategies for Steroid-Refractory cGVHD

(a) **Systemic**

**ECP** – the promising efficacy of ECP (including a clinically significant steroid-sparing effect) and more importantly, without any evidence of deepened immunsupression (and increased infectious risk) make ECP an attractive therapeutic choice [28].

**Sirolimus** – a response rate above 60% with an increased steroidsparing has been reported in small studies. On the other hand, the safety profile of sirolimus does not appear to be as encouraging (interaction potential, thrombocytopenic microangiopathy, hemolysis, infections), and frequent monitoring of blood levels is required [27, 35].

**Mycophenolate mofetil** – reports from small studies suggest reasonable efficacy of this well-tolerated drug when it is added to a standard first-line therapy that has failed [26, 37].

**Rituximab** – in one study with a limited number of patients (n = 21) the use of the anti CD-20 monoclonal antibody was reported to be effective in 70% of steroid-refractory patients with cutaneous and musculoskeletal manifestations of cGVHD. The observation of efficacy of rituximab supports the hypothesis of B-cell involvement in the pathophysiology of cGVHD [29].

- Thalidomide
- Pentostatin
- Daclizumab
- Etanercept
- Pulse intravenous steroids
- Pulse cyclophosphamide
- Hydroxychloroquine
- Thoracoabdominal low-dose irradiation
- Montelukast

(b) **Topical**

- PUVA (Lichenoid cutaneous cGVHD)
- UVB (Lichenoid cutaneous cGVHD)
- UVA1 (Lichenoid cutaneous cGVHD)
- Etretinate (Sclerodermatous cGVHD)
- Topical corticosteroids (Oral GVHD)
- Topical cyclosporine A (Oral cGVHD, ophthalmic cGVHD)
- Intraoral PUVA (Oral GVHD)
- Oral UVB (Oral GVHD)

### 7.4.6 Complications to Avoid

#### 7.4.6.1 Overtreatment

As previously mentioned (see Sects. 3.1 and 3.2), the decision to start GVHD treatment and to adjust its intensity to the patient risk profile can be difficult in
some cases. Systemic treatment must be instituted by a physician experienced in transplantation medicine.

### 7.4.6.2 Infectious Complications

Both GVHD (acute or chronic) and its treatment put a patient at high risk for bacterial, fungal, and viral infections.

#### 7.4.6.2.1 Infectious Complications of aGVHD

Patients with higher grade aGVHD under systemic immunosuppressive therapy are one of the most vulnerable groups in modern medicine. Extremely high risk of various infections (in particular by opportunistic fungi, CMV, and other viruses as well as wide range of pathogenic and opportunistic bacteria) dictates adoption of prophylaxis (e.g., antifungals, Pneumocystis jiroveci prophylaxis) preemptive treatment (e.g., CMV therapy lead by PCR monitoring), and broad spectrum empiric treatment (in case of fever of unknown origin). The detailed antifungal protocols are beyond the scope of this chapter.

#### 7.4.6.2.2 Infectious Complications of cGVHD

Also cGVHD and its treatments lead to profound immunosuppression. Patients with cGVHD should receive prophylactic antibiotic therapy against encapsulated bacteria, Pneumocystis jiroveci; limited evidence supports prophylaxis against fungal pathogens, VZV and HSV [46, 47]. Awareness of the infectious risk and aggressive and prompt treatment of established infections is paramount.

### 7.4.6.3 Drug Toxicity and Interactions

The toxicity of immunosuppressive, antimicrobial, and other drugs and interactions of these are considerable and must be taken into consideration in the decision making process. The topic is beyond the scope of this chapter (more in [48]). Still, the most likely and common toxicity observed in the GVHD setting is that due to systemic corticosteroids. The most common presentations of this toxicity are well recognized: immunodeficiency, hypertension, hyperglycaemia and steroid induced diabetes mellitus, hypokalemia, delayed wound healing, katabolic state, muscle wasting, glaucoma, secondary Cushing syndrome etc.

### 7.4.7 Global Variations

Recent reports [49, 50] have shown that genetic polymorphism in cytokine or other signaling molecule genes can influence the incidence, severity, and outcome of GVHD [51, 52]. As allele frequency varies among different populations, this could be one of the explanations for some reported global variations (e.g., lower incidence of GVHD in the Japanese population).

### Take Home Messages

- More than 40,000 hematopoietic stem-cell transplantations are performed worldwide each year and tens of thousands of transplanted patients are alive long-term [47]. GVHD has become a relatively common problem in the clinical setting. Awareness of its manifestations and a systematic approach will enable prompt and accurate treatment which is critical for improving survival and quality of life of this vulnerable group of patients.
- The management of steroid-refractory aGVHD and cGVHD is currently not standardized and the approaches vary among different centers. The outcomes of this difficult-to-treat patient group are still unsatisfactory.

### References

441

7.4 Graft-Versus-Host Disease


Vitiligo is an acquired skin disorder caused by the disappearance of pigment cells from the epidermis that gives rise to well-defined white patches. The cause of vitiligo is unknown, but currently the most prevailing theories are the genetic and the autoimmune hypotheses [1].

### 7.5.2 Clinical Characteristics and Diagnosis

Vitiligo occurs worldwide in about 1% of the population. There are two commonly recognized forms of vitiligo, i.e., generalized and segmental. The generalized form, vitiligo vulgaris, is characterized by depigmented macules involving both sides of the body in a remarkably symmetrical pattern. The diagnosis of vitiligo vulgaris is made from clinical observations. The clinical manifestations are usually straightforward in a typical case (Fig. 7.5.1).

The patient has depigmentation of the fingers, the feet, or face. The diagnosis is greatly facilitated by the use of the Wood’s lamp. The other form is segmental vitiligo. It is characterized by unilateral, asymmetrical depigmentation. The diagnosis of segmental vitiligo is usually easy (Fig. 7.5.2). The patient will note the onset of depigmentation in an unusual site, part of the face, an extremity or trunk. There are few other diseases that produce unilateral depigmentation without prior skin rashes [2].

### 7.5.3 General Therapeutic Outline

Vitiligo can be cosmetically disfiguring, thus leading to serious psychological problems in daily life. Therefore, vitiligo should never be considered as a trivial cosmetic skin disorder, and the patients should by no means be discouraged from seeking therapy. Rather, a positive approach is recommended involving explaining the nature of the disease process, the likely
prognosis, and the treatment options with their expected results to the patient [3]. Although there is still no therapeutic panacea for vitiligo, there have been significant advances in the therapy of vitiligo in the recent years, and many options may lead to satisfactory results in most patients (reviewed recently in [4, 5, 6]).

7.5.4 Medical Repigmentation Therapies

7.5.4.1 Conventional Therapeutic Approaches

7.5.4.1.1 Psoralens and Ultraviolet Light (PUVA)

Psoralens and exposure to ultraviolet light have long been the standard therapy for the treatment of vitiligo in adults and adolescents. Psoralens and ultraviolet light for vitiligo can be used in several ways. Psoralens can be given orally followed by either exposure to artificial UV (“oral PUVA”) or to solar UV (PUVASOL). Psoralens can also be applied topically followed by exposure to artificial UV (“topical PUVA”) [7]. During PUVA treatment, the patient can note new areas of depigmentation although other areas are repigmenting. This is because PUVA does not prevent the onset or spread of the disease. Therefore, those with stable disease or minimally changing disease are the best candidates. Depigmentation can be very rapid while repigmentation takes months. Therefore, rapidly spreading vitiligo is not optimally treated with PUVA.

Oral PUVA

Oral psoralens have been widely used for the treatment of vitiligo. The agents most often used in current vitiligo treatment are 8-methoxypsoralen (synonyms:
8-MOP, methoxsalen) and 4,5,8-trimethylpsoralen (synonym: trimethylpsoralen) [8–16]. Not all patients respond well to PUVA therapy. A review of the literature suggests that over half will get a moderate or extensive response [17, 18]. The doses of each psoralen must be adjusted carefully. Generally, 8-MOP is used more commonly [19]. The dose of 8-MOP depends on which preparation is used. The old form of 8-MOP requires a dose of 0.3–0.5 mg/kg body weight, taken (with milk or food) 2–4 h before ultraviolet light exposure. A new ultra-micronized form of 8-MOP exhibits greater bioavailability and earlier photosensitization onset time. As a consequence, the recommended dose is only 0.2–0.3 mg/kg body weight, and it should be taken only 1.5–2 h before ultraviolet light exposure [20]. For 4,5,8 trimethylpsoralen, the dose is 0.6–1.2 mg/kg body weight, and it should be taken 2–4 h before ultraviolet light exposure. The dose of UVA must be individualized to each patient. The initial dose is determined by the phototype. Then the dose of UVA is increased by 0.5–1 J/cm² (depending on skin type) every other treatment until minimal asymptomatic erythema (of the depigmented skin) occurs. The subsequent doses should be adjusted to maintain a slight erythema. Patients are treated 2–3 times per week. Treatments are never given on successive days. Preferably, a period of 48–72 h elapses prior to the next treatment. Therapy is continued for a minimum of 3–4 months. The depigmented skin should be examined with a Wood’s lamp to detect the earliest signs of repigmentation. Once repigmentation has started, therapy should be continued until the area is repigmented or progress has stopped. Photographs are invaluable in determining the course of therapy. Precautions during and after PUVA therapy are very important to avoid eye or skin damage. During every PUVA session, total UVA-absorbing/blocking goggles mechanically designed to give maximal ocular protection must be worn. The patient should also wear protective UVA-absorbing wrap-around sunglasses during the daylight for 24 h after PUVA therapy. In addition, to avoid sunburns, patients should not sunbathe for 48 h after therapy. Absolute contraindications for PUVA therapy are skin malignancies, photosensitive diseases, pregnancy, and lactation. Relative contraindications for PUVA therapy are patients younger than 12 years, and cataract, or aphakia [3, 11]. Short-term cutaneous adverse effects of PUVA therapy are increased contrast formation between normal pigmented skin and lesional skin, phototoxic reactions (from erythema to blisters and burns), pruritus, xerosis, and Koebner phenomenon [3, 11]. Short-term systemic adverse effects may include nausea, vomiting, mild epigastric discomfort, headaches, dizziness, (transient) elevation in liver function tests, insomnia, nervousness, fatigue, and drowsiness [3, 11]. Most commonly reported long-term cutaneous adverse effects are lichenification, desquamation, telangiectasia, lentigines or freckles, leukodermapunctata, aging, and wrinkling [3, 11]. Long-term systemic adverse effect is cataract. Because of the possible adverse effects, pre-treatment diagnostic tests such as liver and renal function tests should be repeated annually. Annual eye examinations are also recommended [3, 21]. However there is no evidence to date that in humans PUVA has deleterious effects on the eyes if done properly [22]. Results of studies indicate that UVA does not penetrate the eye lid [23]. Finally, there has been some concern about the carcinogenicity of UVA [11]. It has not been established which is the greater carcinogen, UVA alone, psoralen alone, or the two combined. Studies on patients receiving PUVA for psoriasis have suggested that they have a high incidence of squamous cell carcinomas. In the US there is a disturbing trend for patients who have received PUVA to develop melanoma. This has not been confirmed by long-term studies in Europe [24–27]. If the number of treatments is monitored so that the patient continues treatment only if repigmentation is occurring, the potential risks for skin cancer, almost invariably squamous cell carcinoma, seem small.

PUVASOL

PUVASOL (psoralens with solar ultraviolet A) is commonly used in countries where either sunlight is abundant, or where facilities for artificial UVA are lacking. Contraindications are the same as for oral PUVA therapy. 8-methoxypsoralen (0.3–0.5 mg/kg body weight) or 4,5,8 trimethylpsoralen (0.6–1.2 mg/kg body weight) are administered 2–4 h before sun exposure. The best time for sun exposure is between 11 am and 3 pm. Sun exposure is done in a graded manner. Initial exposures are for 5 min. Treatments are given 2–3 times per week and the exposure dose is increased by 5 min each week to a maximum of 45 min. The dose is held constant when erythema develops. Other precautions are the same as for PUVA therapy [18, 28, 29].
Topical PUVA

Topical psoralens have been used for many years [30–33]. The major advantage of topical PUVA over oral PUVA is lack of systemic toxicity [3, 7]. The patients do not develop nausea, there is no concern about ocular toxicity, laboratory tests to monitor side effects are not necessary. They can be used in children of any age. However they are very potent and tend to cause burns readily. Both local trimethylpsoralen [34] and 8-methoxypsoralen [32, 35] have been used. Currently only 8-methoxypsoralen is available commercially in the United States. It comes in a 1% concentration which is considered too strong [32, 35]. The preparation is diluted 1:10 or 1:100 in petrolatum or like solvent. It is applied in the physician’s office and shortly after the patient is exposed to ultraviolet light. After exposure the affected part is washed with soap and water and a sunblock cream is applied to prevent exposure in the sun. Great care must be taken to prevent overexposure or inadvertent exposure to ultraviolet A in sun light [36]. The dose of ultraviolet A to which the patient is exposed must be monitored with great precision. The starting dose is usually 0.25 J/cm² and increased at each session by 0.1 J/cm² until the treated skin develops a mild pink after the treatment. Without such precautions the probability of painful, blistering burns is very high. Such burns heal often with repigmentation but take weeks to do so. Most patients suggest that the toxicity is not tolerable. Topical PUVA can be useful only for the motivated patient able to follow instructions carefully.

Other Forms of Photo(Chemo)therapy

Khellin plus UVA or phenylalanine plus UVA are not effective and/or are associated with adverse effects. These modalities are not recommended for vitiligo [3].

7.5.4.1.2 Steroids

Topical Steroids

Topical steroids are the most commonly used therapeutic agents. Topical steroids are reported to have a reasonable response rate, possibly up to 50% of those treated [13, 33, 37–46]. In a majority of studies, potent (e.g., betamethasone valerate or betamethasone dipropionate) [37, 46, 47] or very potent (e.g., clobetasol propionate) [33, 38–40, 42–45] steroids have been used. In a meta-analysis, potent steroids were found to be the most effective and safest treatment for localized vitiligo [48]. On the other hand, in a recent study with clobetasol, a very potent steroid, atrophy was reported in three patients (15%) and telangiectasias in 2 (10%) after the eighth week of treatment when approximately 20–30 g of medication had been consumed [45]. In our view, potent steroids have the best benefit/risk ratio and should be used from the onset. If highly potent steroids such as clobetasol propionate are used, they should be applied once daily and for a short period of 2–4 weeks, and then followed by applications of less potent steroids. When initiating a topical steroid treatment for vitiligo, the physician must recall: 1) that he/she will be using the agent for a period of 3–4 months or longer if successful, 2) that the agent will be used around the eyes, in crural folds and over the joints e.g., in locations at high risk of striae and atrophy. The patient should be observed for signs of steroid toxicity although toxicity seems rare when highly potent steroids are limited in their applications. If the patient shows evidence of repigmentation, it is appropriate to continue therapy until no further progress is observed. Photographs can be most useful for such an assessment.

Intralesional Steroids

Others have used injections of steroids into lesions to achieve repigmentation [49, 50]. However a randomized controlled 8-week study showed no statistically significant difference between weekly injection of saline solution and intralesional triamcinolone [50]. In addition, the risk of atrophy is higher with intralesional steroids than with topical preparations. Therefore, intralesional steroids are not recommended in the management of vitiligo.

Systemic Steroids

It has been suggested that a short trial of systemic steroids can halt the progression of vitiligo. In a prospective clinical trial with 14 patients, high-dose methylprednisolone intravenous pulsed therapy administered on 3 consecutive days was demonstrated to
arrest and induce repigmentation in rapidly spreading vitiligo. On the other hand, in the same study, pulsed therapy was not helpful at all in patients with stable, nonprogressive vitiligo [51]. Oral dexamethasone pulse treatment was also found to be effective in arresting progression of vitiligo yet failed to induce satisfactory repigmentation in the great majority of patients [52]. In order to minimize toxicity, some have recommended low doses of oral prednisone [53], while others have recommended mini-pulses of oral betamethasone [54]. The true efficacy of these treatments is not known since the natural course of the disease is variable and difficult to assess in a short time period. Therefore the benefits and toxicity of this therapy must be weighed carefully.

7.5.4.2 Recent Therapeutic Approaches

7.5.4.2.1 Recent Phototherapies

Narrow-Band UVB Phototherapy (NB-UVB)

Narrow-band UVB (NB-UVB) is a more recent form of phototherapy than PUVA, in which the light source emits a light peak at 311–312 nm. NB-UVB does not require the use of a photosensitizer and therefore is easier to use and has less adverse effects than PUVA. NB-UVB was initially used for psoriasis and has since also been found useful for vitiligo [55–62] including childhood vitiligo [56, 62]. In addition, comparative studies have established that NB UVB for vitiligo is at least as efficient as topical [55] or systemic PUVA [63–65]. Very recently, the first randomized controlled trial comparing NB-UVB and PUVA has confirmed that NB-UVB is more efficient than PUVA for vitiligo [66]. Patients with vitiligo who have lesions on the face, darker phototypes, and early response to treatment have a greater chance to achieve satisfactory repigmentation after NB-UVB phototherapy [67]. Patients are treated two or three times a week for a mean period of 3–12 months depending on the series. NB-UVB is usually started at 100–200 mJ/cm² and the fluences are increased to 50 mJ/cm² every second session. The inconvenience of the 308 nm laser are a small spot size (14–30 mm depending on the device) and a high cost (roughly 100,000 €).

308 nm Excimer Laser

The 308 nm excimer laser in vitiligo uses an operational wavelength close to that used in NB-UVB but it has the potential advantage of delivering a high dose of light to a localized affected area, as well as avoidance of unnecessary exposure to the surrounding skin. Several prospective studies have shown the efficacy of this laser in the treatment of vitiligo. In most studies the percentage of treated lesions achieving at least 75% repigmentation is about 30% [68–73]. The rate of repigmentation varies depending upon the anatomic sites: it is very high on UVB-responsive areas such as the face, whereas the extremities and bony prominences show a statistically significant inferior repigmentation rate [73, 74]. Sessions can be performed once to three times weekly since the repigmentation seems to depend on the total number of sessions rather than their frequency [72]. The stability of the repigmentation with time has so far been difficult to evaluate as follow-up of the series is poor; however, a recent series showed no depigmentation of the treated lesions after 1 year [71]. The side effects of the 308 nm excimer laser are limited to erythema and rarely blistering. Patients are treated twice or three times a week for 1–6 months depending on the series. In our experience the 308 nm excimer laser is usually started at 50–200 mJ/cm² and the fluences are increased to 50 mJ/cm² every second session. The inconvenience of the 308 nm laser are a small spot size (14–30 mm depending on the device) and a high cost (roughly 100,000 €).

308-nm Monochromatic Excimer Light

The 308-nm monochromatic excimer light has potential advantages over the 308-nm excimer laser, namely, a larger irradiation area and a lower cost. However there is still little data available about this device. In a pilot study, it was reported that 18/37 patients treated for 6 months with the 308-nm monochromatic excimer light achieved more than 75% repigmentation [75]. In a small comparative study it was found that the 308-nm monochromatic excimer light is more effective than NB-UVB in treating vitiligo lesions [76]. It would be interesting now to determine by a comparative study if the 308-nm monochromatic excimer light is as efficient as the 308 nm excimer laser.
7.5.4.2 Recent Topical Agents

Topical Calcineurin Inhibitors (Tacrolimus, Pimecrolimus)

Topical calcineurin inhibitors were initially used for atopic dermatitis and have since been found useful for vitiligo. Patients are usually treated twice daily with 0.1% tacrolimus or pimecrolimus. The efficacy of tacrolimus for vitiligo was established in adults [77–80] and in children [45, 81]. In particular, a double-blind randomized trial comparing 0.05% clobetasol propionate cream with topical 0.1% ointment in two symmetric vitiliginous lesions in 20 children suggests that tacrolimus is as effective as a single agent as clobetasol propionate [45]. As expected, the efficacy of pimecrolimus for vitiligo seems to be similar to tacrolimus [43, 82, 83]. The best rate of repigmentation with topical calcineurin inhibitors is often observed on sun exposed areas such as the face and the neck where more than 75% repigmentation can be achieved in as much as 68% of patients [80], suggesting that topical calcineurin inhibitors may act synergistically with UV. It was even suggested that tacrolimus might not be efficient in the absence of UV [84], but this finding has not been confirmed elsewhere [85]. The potential advantage of calcineurin inhibitors over steroids is that they do not produce atrophy or other adverse effects [45], implying that they may be particularly useful for younger patients and for sensitive areas of the skin such as eyelids. Despite these positive results, prudence is still in order, especially regarding the risk of carcinogenesis, as long-term follow-up studies are still lacking.

7.5.4.3 Combination Therapies

In the past, there had been encouraging attempts to associate UVA and topical steroids [33, 42, 100]. In the recent years, with the availability of new therapies, there have been additional attempts to combine conventional or targeted phototherapy with topical preparations. As mentioned earlier, the data regarding the adjunction of vitamin D derivatives to either PUVA therapy [87, 89–93], NB-UVB [60, 61, 94–96], or targeted UVB [97, 99], are controversial and do not support their use in vitiligo. The adjunction of topical tacrolimus to NB-UVB phototherapy was not found more effective than NB-UVB alone, but there has been only one study with a small number of patients [101]. Finally, it was reported that concomitant therapy with the 308 nm laser and topical tacrolimus was more effective than laser alone [102]. This was confirmed by a large prospective randomized study [103]. In our view, the association of 308 nm laser and topical tacrolimus is presently the most promising combination therapy available. As for tacrolimus alone, long-term follow-up is still lacking.

7.5.4.3 Antioxidant Therapies

7.5.4.3.1 Pseudocatalase

In a pilot study with 33 patients, 80% of individuals seemed to improve with applications of topical pseudocatalase and exposure to ultraviolet light [104]. However since the study was uncontrolled, it is uncertain whether the observed repigmentation should be attributed to pseudocatalase. In addition, others have not confirmed that pseudocatalase was beneficial for vitiligo [105]. Recently, a new antioxidant formulation containing Cucumis melo superoxide dismutase and catalase (Vitix®) has been introduced for the treatment of vitiligo. However, it was reported recently that Vitix® does not have the capacity to remove H₂O₂ from the skin and does not improve facial vitiligo [106].
7.5.4.3.2 Ginko Biloba

A randomized placebo-controlled trial has evaluated the efficacy of G. Biloba extracts in 52 patients with limited slow-spreading vitiligo. A repigmentation of at least 75% was observed in 40% of patients treated with G. Biloba vs. 9% in the control group [107]. If these results were to be confirmed, G. Biloba could become a therapeutic option for limited slow-spreading vitiligo.

7.5.5 Surgical Repigmentation Therapies

Surgical techniques (reviewed in: [108–113]) are an alternative for patients with refractory, but stable vitiligo. They rely on the same principle: to repopulate depigmented skin lesions with autologous melanocytes from normal epidermis. Normal epidermis can be obtained from different regions. The most convenient is the gluteal region, where any change induced by the harvesting procedure can be easily covered. Several surgical methods are available depending on the type of graft. Tissue-grafts consist of the simple transfer of epidermis or skin, sampled and implanted as it is. Cellular grafts consist of the transplantation of disaggregated epidermal cells. Cellular grafts can be further classified in two categories according to whether cells are cultivated or not.

7.5.5.1 Tissue Grafts

There are three types of tissue grafts: full-thickness punch grafting, suction blister grafting, and split-thickness grafting. Tissue grafts cannot (suction blister grafts, punch grafts) or hardly (split-thickness grafts) be expanded. Hence they can only be used for the treatment of limited areas and multiple procedures may be needed to achieve desirable rates of repigmentation.

7.5.5.1.1 Full-Thickness Punch Grafting (“Minigrafting”)

Autologous minigrafting or punch grafting involves removing 1–2 mm skin specimens, using a punch biopsy knife, from selected pigmented autologous donor sites and transplanting them to depigmented acceptor sites from which similarly obtained grafts have been extracted [114–120]. Repigmentation around punch grafts usually starts 2–3 weeks after graft placement. Coalescence of pigment from all punch grafts occurs within 4–6 months. Common adverse effects are cobblestoning and scar formation at the donor site.

7.5.5.2 Cellular Grafts

The potential advantage of techniques based on cell separation and/or culture is to allow the treatment of larger lesions than techniques based on tissue grafts.
The main limitation of these techniques is that they require more time, personnel, and equipment than tissue grafts.

**7.5.5.2.1 Transplantation of Noncultured Autologous Epidermal Cell Suspensions**

Transplantation of noncultured epidermal suspensions involves injecting an epidermal suspension with melanocytes and keratinocytes from normally pigmented donor skin previously prepared by trypsinization into denuded vitiliginous acceptor sites [131–138]. Using this technique, it is possible to graft lesions up to 10 times larger than the donor site. The effectiveness of this surgical technique was confirmed recently by a large randomized, placebo-controlled study [131].

**7.5.5.2.2 Transplantation of In Vitro-Cultured Pure Melanocytes**

Transplantation of in vitro-cultured pure melanocytes involves transplanting autologous pure melanocytes previously cultured in vitro from normally pigmented donor skin into the denuded depigmented acceptor skin [139–142].

**7.5.5.2.3 Transplantation of In Vitro-Cultured Autologous Epidermis**

Transplantation of in vitro-cultured autologous epidermis involves transplanting autologous thin sheets of epidermis previously cultured in vitro from normally pigmented donor skin into the denuded depigmented acceptor skin [143–147]. In two large studies of transplantation of in vitro-cultured autologous epidermis, the average repigmentation rate was 77% [143, 144].

**7.5.5.2.4 Comparison of Cell Grafting Techniques**

Transplantation of noncultured autologous epidermal cell suspensions is the easiest and least expensive technique since it does not require in-vitro cell culture. In-vitro cultured autologous epidermis can provide more cells for the treatment of larger lesions. Using this approach, lesions of up to 500 cm² can be treated with melanocytes generated from biopsy specimens as small as 1 cm². Major disadvantages are more complex infrastructure, longer time, and higher cost.

**7.5.5.3 Choice of A Surgical Technique**

The surgical techniques of melanocyte transplantation for vitiligo are summarized in Table 7.5.1. The choice of a technique should take into account, the surface to be treated, the surgical experience of the user, and the availability of cell culture facilities. Minigrafting and noncultured epidermal cell suspensions seem to represent the best compromise, respectively for limited and extensive lesions.

**7.5.6 Other Therapies**

**7.5.6.1 Depigmentation**

For patients with extensive areas of depigmentation (more than 80%) and/or disfiguring lesions of the face, who do not respond to repigmentation therapies, depigmentation of the residual melanin should be considered. These patients should be informed that in case of success, removal of residual pigmentation is permanent and irreversible. On the other hand, patients should also be warned that repigmentation may occur, even after total depigmentation has been achieved. During and upon completion of depigmentation, the patients must be advised to minimize sun exposure and to apply sunscreens.

**7.5.6.1.1 Bleaching Agents**

Depigmentation is accomplished by sparing applications of a monobenzylether of hydroquinone (MBEH), a potent melanocytotoxic agent, in a 20% cream. The treatment should start with a single daily application to a test spot. If no adverse effects occur, greater skin
<table>
<thead>
<tr>
<th>Category</th>
<th>Technique</th>
<th>Harvesting of grafts</th>
<th>Preparation of recipient area</th>
<th>Indications</th>
<th>Success rate (%)</th>
<th>Side-effects (D: donor site R: recipient site)</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue grafts</td>
<td>Suction blister grafts</td>
<td>Vacuum pump</td>
<td>Liquid nitrogen</td>
<td>Limited lesions</td>
<td>73–88</td>
<td>R: Hyperpigmentation</td>
<td>Easy, safe, inexpensive</td>
<td>No scar formation</td>
<td>[6–23]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dermabrasion Laser</td>
<td>Segmental lesions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Facial lesions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Eyelids, lips, bony prominences</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Split-thickness grafts</td>
<td>Shave biopsy</td>
<td>Dermabrasion Laser</td>
<td>Multiple/large lesions</td>
<td>78–91</td>
<td>R: Thick margins, partial loss, milia-like cysts</td>
<td>No scar formation</td>
<td></td>
<td>[24–28]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Extremities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Eyelids, lips</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Full-thickness punch-grafts</td>
<td>Punch biopsies</td>
<td>Punch biopsies Laser</td>
<td>Limited lesions</td>
<td>68–82</td>
<td>D: Scarring</td>
<td>Easiest and least expensive method</td>
<td>Time consuming Regrafting between punches may be needed</td>
<td>[19, 29–36]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Segmental lesions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lips, pams/soles, fingers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellular grafts</td>
<td>Epidermal cell suspension</td>
<td>Shave biopsy</td>
<td>Liquid nitrogen</td>
<td>Extensive lesions</td>
<td>67–85</td>
<td>R: Long lasting erythema (dermabrasion)</td>
<td>Larger areas treatable</td>
<td>Special equipment</td>
<td>[39–47]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dermabrasion Laser</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cultured melanocyte suspension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cultured epidermal grafts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**References:** [6–23] [24–28] [19, 29–36] [39–47] [48–56] [57–67]
areas can be gradually treated with a frequency of one to twice daily. Depending on the residual pigmentation, 6 months to 2 years may be required to complete the therapy. Not all patients respond but more than 50% can expect a markedly improved outcome [148]. The most common adverse effect of MBEH is allergy [149].

7.5.6.1.2 Laser Therapy

Another form of depigmentation therapy for vitiligo has also been developed, making use of a Q-switched ruby laser [150].

7.5.6.2 Micropigmentation

Tattooing or micropigmentation has been found to have some use in the treatment of vitiligo. It seems especially useful for coloring the mucous membranes of darker colored individuals who have vitiligo. The lips of these individuals become pink when affected by vitiligo. The normal color is gray-brown. Micropigmentation can restore the lips to a more normal appearance although the color match is not perfect [151, 152]. Micropigmentation can also be helpful for coloring the areolas. However, micropigmentation is not suitable for other skin lesions because it does not follow the seasonal variation of skin color.

7.5.6.3 Camouflage

Camouflage with decorative cosmetics can be recommended for all patients, particularly in patients whose quality of life is impaired. Patients with minor involvement of the face also benefit from camouflage [153].

7.5.6.4 Sun Protection

Loss of melanin in vitiliginous lesions increases the risk of sunburn. In the case of sun exposure, sunscreens with high sun protective factor should be applied on vitiligo lesions. In order to limit the contrast between depigmented and normal skin, it is better to use these sunscreens simultaneously on the normally pigmented skin.

7.5.6.5 Counseling

Studies on the psychosocial impact of vitiligo have suggested that patients suffer from low self-esteem, poor body image, and a poor quality of life. The burden on the quality of life caused by vitiligo has been quantified and specific areas of patients’ lives which are most affected by the disease have been identified [154]. The physician can care for most of these and needs to be empathetic about the desire for therapy. It is useful for the physician to consider what he would do if he had vitiligo depigmenting his face and hands. There are a few patients who are sufficiently disturbed, that formal psychiatric counseling is indicated.

7.5.7 Future Directions

Several innovative approaches are being explored. Prostaglandins play an important role in melanocyte proliferation and melanogenesis. In a small open-labeled study, application of a prostaglandin E2 gel induced repigmentation of vitiligo in a majority of patients [155]. This encouraging report needs to be confirmed by larger and comparatives studies. New sources of light are also under investigation. Helium-neon laser irradiation (632.8 nm) induces partial

Table 7.5.2 Treatment recommendations for vitiligo

<table>
<thead>
<tr>
<th>Type of vitiligo</th>
<th>1st choice therapy</th>
<th>Alternative therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized (up to 10% of BSA affected)</td>
<td>Topical calcineurin inhibitors Topical corticosteroids agents</td>
<td>Targeted UV-B phototherapy ± calcineurin inhibitors Melanocyte transplantation</td>
</tr>
<tr>
<td>Generalized (11–80% of BSA affected)</td>
<td>NB-UVB</td>
<td>Oral PUVA</td>
</tr>
<tr>
<td>Extensive (more than 80% of BSA affected)</td>
<td>Topical depigmentation therapy (20% MBEH)</td>
<td>Topical depigmentation + Q-switched ruby laser treatment</td>
</tr>
</tbody>
</table>
repigmentation in segmental-type vitiligo [156]. Recently, it was suggested that UVA alone, without psoralens, may be of some therapeutic value in vitiligo [157].

Take Home Message

> In the past 10 years, new methods of treating vitiligo have emerged: NB-UVB therapy, targeted phototherapy, and topical calcineurin inhibitors. Refinement of surgical techniques has also continued. These advances have led to new treatment schemes. Current recommendations regarding first and alternative choices, according to the severity of disease, are summarized in Table 7.5.2. In all cases, advice regarding the use of camouflage and sunblocking agents should always be given and psychological support should be provided. However, at present, among available studies, most are uncontrolled pilot studies or case reports and only a few are randomized controlled trials. More randomized controlled trials should be performed in the future in order to better identify one single treatment modality as the most effective for a particular form of vitiligo.

7.5.8 Global Variations

Vitiligo occurs in all continents. It is obvious that vitiligo developed in dark pigmented patients causes many problems and represents a much larger burden for the patients in the socioeconomic environment. Bleaching agents and camouflage techniques are therefore more intensely used in these populations. However, there exist no global variations in the principal approaches for treatment.

References


7.5 Vitiligo


7.6 Sarcoidosis

7.6.1 Etiology and Pathophysiology

Sarcoidosis is a chronic, systemic disease of unknown etiology, characterized by noncaseating granulomas affecting many organs, most commonly the lung, but also skin. Women are more commonly affected. Incidence is high among Scandinavians (64 cases per 100,000) and low among Polish (3 cases per 100,000). In the USA, it is higher among African Americans (35.5–64 cases per 100,000 population) than among Caucasians. Proposed antigens may be infectious, environmental, and autoantigens. The most common infectious agent implicated is Mycobacterium tuberculosis, but the evidence is conflicting. Environmental antigens include metals (i.e., zirconium), organic dusts (i.e., pollen), and inorganic dusts (i.e., talc). Heat shock protein has also been incriminated. Pathogenesis has been related to an increased production of Th1-like cytokines, including IL-2, tumor necrosis factor (TNF-α), and interferon gamma (IFN-γ). However, cutaneous anergy to tuberculin intradermal testing occurs in two thirds of patients, and an increase in B-cell activity with hypergammaglobulinemia is noted in 50% of patients with immune-complex formation [1].

7.6.1.2 Clinical Characteristics and Diagnosis

All organs may be involved with a variable clinical presentation. Although the onset is insidious, 30% of patients have fever, fatigue, and weight loss. Most of them have lung involvement, and one third have palpable lymph nodes. Anterior uveitis is common and is sometimes associated with fever and parotid swelling (Heerfordt syndrome). The nervous system involvement is rarer with the palsy of the facial nerve being the most frequent finding. Heart involvement occurs in 5% of patients. Elevated liver function tests, arthritis, anemia, leukopenia, hypercalcemia, diabetes insipidus, and renal failure may be also observed.

Skin is affected in 25% of patients and may be isolated or accompanying systemic involvement. Lesions are specific and nonspecific. The former consists of macules, papules, nodules, plaques, and subcutaneous infiltrations. Infiltration of old cutaneous scars with
sarcoid granuloma in the active phase of disease, known as scar sarcoidosis, may also occur. Histopathology reveals noncaseating granulomas, with a very scanty lymphocytic component (naked granulomas). Erythema nodosum (EN) is the main nonspecific cutaneous manifestation. The association with unilateral or bilateral hilar and/or right paratracheal lymphadenopathy, anterior uveitis, and/or polyarthritis constitutes the Löfgren syndrome.

Diagnosis of the skin manifestations is based on the histopathological identification of the noncaseating granulomas without acid-fast bacilli and the absence of the features of foreign body granulomas. Cutaneous tuberculosis and, in endemic areas, tuberculoid leprosy are the main differential diagnoses.

### 7.6.1.3 General Therapeutic Outline

Although the mechanisms involved in sarcoidosis remain incompletely understood, granuloma formation commands the clinical course and therapeutic response. Its suppression results in preservation of organ function and prevention as much as possible of the fibrotic outcome. The progression of granuloma varies greatly and tissues respond differently to different drugs, with skin and mucosal disease responding usually to antimalarials better than other location of the disease. As long-term corticosteroids are the first line of therapy, side effects of their systemic use should be carefully evaluated before commencing such therapy.

### 7.6.1.4 Current Established Therapies

Topical corticosteroids may be used in skin lesions as first-line therapy, either in occlusion or not. High-potency preparations should be used with caution, given the frequent facial location of the lesions. Intralesional triamcinolone (2–5 mg/mL) is used for deep and resistant nodules. There is, however, no evidence, proving that they are really effective [2].

Systemic corticosteroids are the treatment of choice for patients with neurologic, cardiac, or ocular involvement, hypercalcemia and symptomatic stage II and all stage III pulmonary disease, and, despite the lack of randomized-controlled data [2], for cutaneous sarcoidosis. The usual dose is 30–40 mg of prednisone daily for 2–3 months, tapering over 1 year down to 10–20 mg every other day. Higher doses are rarely needed. Löfgren syndrome is an acute self-limited process, but nonsteroidal anti-inflammatory drugs can be useful. Most of systemic therapies for cutaneous sarcoidosis are extension of the drugs used for pulmonary sarcoidosis.

Antimalarials should be considered as the second line of treatment, especially in patients with disfiguring lesions. The maximum dosage of chloroquine and hydroxychloroquine should not exceed 3.5 and 6.5 mg/kg/day due to ocular toxicity [2].

Although there are no randomized-controlled studies on methotrexate in cutaneous sarcoidosis, studies suggest that it might be useful as a steroid-sparing drug [2]. Doses vary from 10 to 30 mg/week.

Azathioprine and chlorambucil are also said to be effective.

### 7.6.1.5 Experimental Approaches

Other drugs include cyclosporine, oral isotretinoin (0.5-1 mg/Kg/day) allopurinol (100–300 mg/day), minocycline (200 mg/day), doxycyclin (200 mg/day), transilat (300 mg/day for 3 months), pentoxyfilline, melatonin (20 mg/day), leflunomide [4], mycophenolate mofetil, and topical tacrolimus, and PUA and photodynamic therapy (4). A surgical approach for limited, disfiguring lesions such as those occurring in lupus pernio with pulse dye and CO₂ laser, has been also suggested.

Thalidomide (100–200 mg/day) for 3 weeks tapered to 50–100 mg/day for several weeks, then to 50 mg/day every other day for months has been said to be effectual.

More recently, anti-TNF-α drugs including infliximab, etanercept and adalimumab proved in anecdotal reports to be effective for refractory sarcoidosis [5]. However, paradoxically, cutaneous and pulmonary sarcoidosis may develop also during treatment with all three TNF-α inhibitors [6] (personal observation). Discontinuation of anti-TNF-α therapy usually leads to recovery.
7.6.1.6 Complications to Avoid

Diabetes, increased susceptibility to infections, osteoporosis with avascular necrosis of bone, neuropsychiatric changes, and generalized skin wasting with emphysema leading to fatal heart failure (personal observation) are the possible side-effects of long-term administration of oral corticosteroids.

Ocular complications are the main side-effects of antimalarials, especially chloroquine. They range from corneal opacity to irreversible retinopathy. Nausea and vomiting, irritability and depression, fatigue and pigmentation are other side-effects.

Bone-marrow suppression, nausea and vomiting are possible side-effects of methotrexate, but hepatotoxicity is by far the commonest harm (up to 25%), especially in people with latent HCV (or HBV) infection. Hepatotoxicity may occur at any dose and at any moment of the treatment. A pulmonary syndrome with fever, cough, dyspnea, and pulmonary infiltrate is a rare event.

7.6.2 Granuloma Annulare

7.6.2.1 Etiology and Pathophysiology

Etiology and pathogenesis of granuloma annulare are unknown. Possible causes are acid-fast bacilli, viruses, insect bites, trauma, sun exposure, and thyroiditis. Pathogenetic hypotheses vary from cell-mediated immunity to immunocomplex vasculitis. A hereditary component has been shown in some cases. Women are affected twice as often as men.

The possible association with underlying diseases (diabetes, thyroid disease, malignancy especially lymphomas) although not adequately supported by the available evidence supported by the available evidence [7], should be evaluated.

7.6.2.2 Clinical Characteristics and Diagnosis

Four types are distinguished: localized, generalized, subcutaneous, and perforating. Actinic granuloma is probably a separate entity. The localized type is the most common followed by the generalized one, while the other types are rare. In the localized type, the disease starts with small flesh-colored papules that arrange in annular plaques with a depressed center. The regions mostly affected are the extensor aspects of the limbs including feet and hands.

The typical histopathologic features include palisaded granulomas with macrophages surrounding acellular necrobiotic areas in which collagen bundles are thinned or have a pale homogeneous appearance. Mucin is abundant.

Annular lichen planus, erythema annulare centrifugum, erythema elevatum diutinum, erythema migrans, and tuberculoid leprosy should be considered as differential diagnosis.

Laboratory tests are noncontributory.

7.6.2.3 General Therapeutic Outline

The localized type is self-limited and the patient should be only reassured. The rare symptomatic lesions can be treated by various methods, but the level of evidence is low. The generalized type tends to persist and often requires treatment. Also in this case, however, the available evidence cannot support any of the proposed therapies.

7.6.2.4 Current Established Therapies

Potent topical corticosteroids are usually employed with or without occlusion for 4–6 weeks or intralesionally in the localized type [8]. Cryotherapy has also been advocated [9]. The generalized type can be treated
with PUVA or UVA1 (340–400 nm) [10]. A review of the literature on isotretinoin reports its use at 0.5–1 mg/kg/day, primarily in the disseminated form of the disease. Lower doses are often needed in response to drug-related liver function test elevations.

### 7.6.2.5 Experimental Approaches

Topical tacrolimus, imiquimod, vitamin E, cryosurgery, and CO₂ laser have been suggested by anecdotal reports for the localized type. For the generalized type, dapsone, antimalarials, systemic steroids, pentoxifylline, hydroxychloroquine, chlorambucil, cyclosporine, clofazimine, fumaric esters, interferon-gamma, potassium iodide, and nicotinamide and TNF-inhibitors such as infliximab [11].

### 7.6.2.6 Complications to Avoid

Secondary dyschromia may follow cryotherapy. Topical corticosteroids should be avoided on facial lesions for their well-known atrophogenic properties. Systemic corticosteroids have the well-known side-effects. Isotretinoin should be reserved for patients with disseminated or refractory generalized cases and excluded in pregnant and breastfeeding women. Potential serious adverse effects associated with its use require careful monitoring and precise guidelines [12].

### Take Home Message

- In the absence of randomized-controlled studies, the risk/benefit ratio should be considered in all cases.

### 7.6.3 Necrobiosis Lipoidica

#### 7.6.3.1 Etiology and Pathophysiology

About 20% of patients with necrobiosis lipoidica have diabetes mellitus, but only a minority (0.3%) of diabetics have the disease. In nondiabetic patients, the etiology is unknown [13].

#### 7.6.3.2 Clinical Characteristics and Diagnosis

The patient presents with one or multiple sclero-atrophic plaques on the shin(s). Other locations are rare. The plaque is centered by a yellow-brownish depression surrounded by a polycyclic raised and reddish border. Over time, ulceration may supervene.

Diagnosis is clinical and histological, although biopsy is not always advisable for the risk of persistent ulceration. Granulomas are interstitial and palisaded, involve the subcutaneous tissue, and are admixed with areas of collagen degeneration. Thickening of the blood vessel walls characterizes the form associated with diabetes (microangiopathy). Differential diagnosis includes mainly granuloma annulare which never ulcerates, Mieschers’ disciform granulomatosis, a possible variant of sarcoidosis, and the actinic granuloma.

#### 7.6.3.3 General Therapeutic Outline

In the absence of any successful randomized controlled studies, rational treatment is limited only to the control of diabetes when present.

#### 7.6.3.4 Current Established Therapies

Topical treatments include potent corticosteroids, often under occlusion and isotretinoin. Topical PUVA proved effective in 37% of cases, but 13% of patients worsened and in no case was skin thickness increased [14].

Systemic treatment includes a number of drugs. Aspirin was tried in a randomized controlled study [15] but proved to be ineffective. Cyclosporin A (3–4 mg/kg/day) has been successful in two patients [16]. Systemic corticosteroids were effectual in a small series [15], but their effect is limited to the border of the lesions, as it occurs with topical corticosteroids, which is easier and less dangerous to use.

Surgical removal and grafting have been used, but recurrence may occur. Hyperbaric oxygen has also been used [17].
7.6.3.5 Experimental Approaches

Mycophenolate mofetil has been used (1 g/day, then reduced to 0.5 g) in one ulcerated case, with complete healing of ulcers in 1 month [18]. Tacrolimus in 0.1% ointment was effective in one patient in whom ulceration resolved in 1 month [19]. UVA1 (15–51 exposures given 3–5 times weekly) have been of some benefit in a small series [20]. Pentoxifylline, niacinamide, stanozolol, granulocyte-macrophage colony-stimulating factor, and topical tretinoin have been used on anecdotal base.

7.6.3.6 Complications to Avoid

Besides the well-known complications of long-term corticosteroid treatment, the risk/benefit ratio of all suggested systemic therapies is probably too high.

Take Home Message

- In the absence of accepted guidelines, topical treatment is recommended.

7.6.4 Necrobiotic Xanthogranuloma

7.6.4.1 Etiology and Pathophysiology

The aetiopathogenesis is unknown. The disease occurs between 50 and 60 years of age, regardless of gender.

7.6.4.2 Clinical Characteristics and Diagnosis

The disease most commonly affects the periorbital area (Fig. 7.6.1), involving the ocular adnexa in 80% of cases [24], but also the extremities and trunk. The lesions are indurated, violaceous telangiectatic nodules or plaques. Usually the nodules are not tender and in 42% of cases develop atrophy or ulceration in the center [25]. Histopathology shows extensive areas of necrobiosis with a prominent granulomatous infiltrate in the dermis and subcutis, containing bizarre angulated foreign-body giant cells, together with Touton-type giant cells and foam cells and cholesterol clefting. Most patients exhibit a slowly progressive course. In more than 70% of cases there is a monoclonal gammopathy. Either κ- or λ-IgG. Over 17 years, 38% of patients develop a malignancy that may consist of multiple myeloma (15%), chronic lymphocytic leukemia, and Hodgkin and non-Hodgkin lymphomas. Systemic involvement of the respiratory tract and heart have been reported with increased frequency in the recent years [21]

7.6.4.3 General Therapeutic Outline

The treatment of necrobiotic granuloma is varied, largely palliative and often unsuccessful. Patients should undergo life-long follow-up to detect the development of associated malignancy [22].
7.6.4.4 Current Established Therapies

The treatment options reported in the literature include palliative reduction of the skin lesions and treatment of the underlying disease. The latter may induce some improvement in the cutaneous disease but no randomized controlled trials have been reported. Topical or intraleisional steroids can be used if the lesions are of reduced size [21, 23]; several patients may respond to systemic steroids, although the lesions often recur [21, 24]. Interferon-α, radiotherapy, Co2 laser and surgery have been tried. Surgery has a high rate of recurrence (40%) [22]. Chemotherapy agents (chlorambucil, cyclophosphamide, melphalan, etoposide) have been used with variable results [25, 26] if the paraprotein load needs to be reduced. A rapid progression of the lesion under treatment with melphalan has even been reported [27].

Chemotherapy agents (chlorambucil, cyclophosphamide, melphalan, etoposide) have been used if the paraprotein load need to be reduced with variable results [25, 26]. A rapid progression of the lesion under treatment with melphalan has even been reported [27].

7.6.5 Miscellanea

7.6.5.1 Rheumatoid Nodule

Rheumatoid nodules are subcutaneous granulomatous nodules occurring, on extensor surfaces of the limbs in about 16% of patients with rheumatoid arthritis. Histopathology reveals a palisading granuloma with fibrinoid necrosis. They can be dissected, with frequent relapses, or injected with triamcinolone. There are reports of their accelerated production during therapy with methotrexate, etanercept, and infliximab [28].

7.6.5.2 Elastolytic Granuloma

Elastolytic granuloma is a rare entity characterized by annular patches with elevated borders and central atrophy in sun-exposed areas. Histopathology reveals a nonpalisading granuloma with loss of elastic tissue and elastophagocytosis by multinucleate giant cells. Treatments including topical steroids, topical pimecrolimus and oral tranilast, antimalarials give variable response [29]. Paradoxically, narrow-band ultraviolet B irradiation and PUVA have been reported as effective [30].

7.6.5.3 Metastatic Crohn’s Disease

Granulomatous lesions on skin or mucosa affect about 0.5% of Crohn’s patients. They show sarcoid-type granulomas, have a lengthy course, and can correlate with disease activity. Treatment is challenging. A combined medical treatment (metronidazole with prednisolone) can be effective [31]. Surgical treatment should be reserved for non responding cases. Cyclosporine and infliximab have also been tried on anecdotal basis [32, 33].

7.6.5.4 Granulomatous Rosacea and Perioral Dermatitis

In some patients, papulo-pustules acquire a yellow-brownish color, harder consistence, and lengthy course. Histopathology reveals a tuberculoid/foreign body granuloma. Treatment is systemic and includes

<table>
<thead>
<tr>
<th>Take Home Message</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basically, the therapy of necrobiotic xanthogranuloma is largely palliative or is that of the underlying disease.</td>
</tr>
</tbody>
</table>
doxycycline and metronidazole. The latter is rarely used in the USA.

7.6.5.5 Lupus Miliaris Disseminatus Faciei

It is a rare, chronic, inflammatory dermatitis of the central face with red-to-yellow-brown papules, particularly on and around the eyelids. Lesions may occur singly or in crops. It may either be a variant of granulomatous rosacea or a distinct entity. Histopathology shows an epithelioid cell granuloma, often with perifollicular involvement, sometimes with neutrophilic abscesses and caseation. Etiology and pathogenesis are unknown even though mycobacteria and Demodex folliculorum have been incriminated. Reported therapies include low-dose prednisone, dapsone, tetracyclines, chloroquine, and isotretinoin. No randomized controlled studies exist. After a 1–3-year course, it resolves spontaneously.

7.6.5.6 Foreign Body Granulomas

They mostly include the reactions to ruptured cysts, marine inanimate or living particles and materials used for soft tissue implants. The latter include non resorbable materials (silicone, paraffin, etc) or even resorbable substances (hyaluronic acid, bovine collagen, etc). The former invariably produce granulomas and rejection of the implant for up to 20 years following implantation. Hyaluronic acid produces them more rarely [34]. Histopathology is discriminating. Treatment is deceiving and relies upon intraleisonal and systemic steroids, minocycline, and immunomodulatory agents, such as cyclosporin. Isotretinoin has been advocated [35].

7.6.5.7 Cutaneous Granulomas Associated with Primary Immunodeficiency Disorders and Lymphomas

Common variable immunodeficiency is a primary immunodeficiency characterized by hypogammaglobulinemia, poor antibody responses, variable T-cell abnormalities, and recurrent bacterial infections. A not uncommon complication is granuloma of the lungs, spleen, liver, and/or skin. Cutaneous granulomas, mainly of the sarcoid-type, may also develop in the setting of an underlying systemic Hodgkin’s and non-Hodgkin’s lymphoma [36]. The treatment of cutaneous granulomas in these immunosuppressed patients remains problematic. Antibiotics, intravenous immunoglobulins, antifungal agents, systemic and intraleisonal steroids, IFN-γ, cyclosporine, methotrexate, hydroxychloroquine, localized radiation therapy, and surgical excision gave variable results. Very recently, TNF-α inhibitors have been successfully used in anecdotal cases [37]. Further controlled studies are needed to determine the best management of these conditions in the setting of immunodeficiency.

7.6.5.8 Interstitial granulomatous dermatitis

Interstitial granulomatous dermatitis with arthritis is a rare condition characterized by chord-like lesions or annular, violaceous plaques on the trunk and limbs. It may be associated with drugs or autoimmune diseases. Treatment has not yet been codified and is based primarily on antiinflammatory drugs such as systemic steroids, antimalarials and FANS. Topical steroids can be used if lesions are limited in extension. Paradoxical effects have been described with anti-TNFα agents both triggering and improving the condition. Spontaneous resolution occurs [38].

7.6.5.9 Global Variations

Fumarates are used especially in Germany and reported to be effective for the treatment of recalcitrant non infectious granulomatous diseases [39]. In particular, sarcoidosis, disseminated granuloma annulare and necrobiosis lipoidica have been successfully treated in a small series of patients.

References

Part VIII

Metabolic Diseases
8.1 Etiology and Pathophysiology

The porphyrias are metabolic disorders arising from a predominantly hereditary catalytic deficiency of the second to eighth enzyme involved in the porphyrin-heme biosynthetic pathway (Fig. 8.1.1) [1–3]. Mutations in any of the genes encoding these enzymes can lead to a pathological accumulation and measurable excretion of porphyrins and/or porphyrin precursors due to enzyme dysfunction. Except for Porphyria cutanea tarda (PCT), all types of porphyria show a Mendelian inheritance pattern (Table 8.1.1) [4].

The porphyrias comprise eight different types, in detail: PCT; erythropoietic protoporphyria (EPP); congenital erythropoietic porphyria (CEP); hepatoerythropoietic porphyria (HEP); acute intermittent porphyria (AIP); variegate porphyria (VP); hereditary coproporphyria (HCP); and δ-Aminolevulinic acid dehydratase (ALAD) deficiency porphyria [1–3]. Each type is caused by a particular single-gene defect that underlies the specific enzymatic dysfunction [4] (Table 8.1.1).

8.1.1.1 Enzymatic and Molecular Defects Underlying the Porphyrias

8.1.1.1.1 Porphyria Cutanea Tarda (PCT)

PCT (OMIM 176100) is the most frequent type of porphyria worldwide and results from a decreased catalytic activity of uroporphyrinogen decarboxylase (UROD), the fifth enzyme in heme biosynthesis (Fig. 8.1.1) [1, 2, 5].

According to the major site of expression of UROD, at least two types of PCT can be distinguished: a sporadic (acquired) variant, designated type I PCT, in which the enzymatic deficiency is exclusively expressed in the liver, and a familial (hereditary) variant, designated type II PCT, in which the catalytic enzymatic defect is detected in all tissues (Table 8.1.1). Currently, the ratio between type I and type II PCT is estimated to be approximately 3:1–4:1 [1, 2].
Of note, not every PCT patient with a positive family history will necessarily be suffering from type II PCT. Recently, several families were reported in which more than one individual were unequivocally affected with PCT. While these individuals revealed the typical clinical and biochemical characteristics of overt disease, normal UROD activities were measured in red blood cells. This latter variant of the disease has been designated as type III PCT, and, in sum, there is increasing evidence that some facets of the etiology of PCT are not yet completely elucidated [5].

Recently, the molecular mechanisms underlying the cutaneous symptoms in EPP have been uncovered. It is now clear that only those individuals who not only inherit a heterozygous \( \text{FECH} \) gene mutation on one parental allele but also a specific intronic \( \text{FECH} \) polymorphism on the other parental allele will develop skin symptoms [6]. The identification of the molecular mechanisms underlying the manifestation of photosensitivity in EPP certainly has to be considered a milestone in porphyria research.

### 8.1.1.1.2 Erythropoietic Protoporphyria (EPP)

EPP (OMIM 177000) arises from an autosomal dominantly inherited deficiency of ferrochelatase (\( \text{FECH} \)), the last enzyme in heme biosynthesis (Fig. 8.1.1).

### 8.1.1.1.3 Congenital Erythropoietic Porphyria (CEP)

With approximately 150 cases reported to date, CEP (OMIM 263700) is a very rare, autosomal recessively
8.1 The Porphyrias

8.1.1.4 Hepatoerythropoietic Porphyria (HEP)

HEP (OMIM 176100), the homozygous variant of hereditary PCT, is caused by a drastic deficiency of UROD, resulting from homozygous or compound heterozygous mutations in the UROD gene (Table 8.1.1). The disease is extremely rare and has been reported only in the United States of America and Europe [1, 2, 8].

8.1.1.5 Acute Intermittent Porphyria (AIP)

Except for South Africa and Chile, AIP (OMIM 176000) is the most frequent type of acute porphyria worldwide. This autosomal dominantly inherited disorder is characterized by a deficiency of porphobilinogen deaminase (PBGD), the third enzyme in heme biosynthesis (Fig. 8.1.1) [1, 2].

8.1.1.6 Variegate Porphyria (VP)

Due to founder effects, the disease is particularly frequent in South Africa and Chile where it represents the most frequent type of acute porphyria. VP (OMIM 176200) is characterized by an autosomal dominantly inherited deficiency of protoporphyrinogen oxidase (PPOX), the seventh enzyme in the pathway of heme biosynthesis (Fig. 8.1.1) [1, 2, 9].

8.1.1.7 Hereditary Coproporphyria (HCP)

HCP (OMIM 121300) is a very rare, autosomal dominantly inherited disease, characterized by a deficiency of coproporphyrinogen oxidase (CPOX), the sixth enzyme in the porphyrin-heme biosynthetic pathway (Fig. 8.1.1) [1, 2].

8.1.1.8 δ-Aminolevulinic Acid Dehydratase (ALAD) Deficiency Porphyria

This autosomal recessively inherited porphyria variant is extremely rare and results from a profound deficiency of δ-aminolevulinic acid dehydratase (ALAD), the second enzyme in heme biosynthesis. With less than ten cases reported worldwide, however, ALAD deficiency porphyria (OMIM 125270) does not play an important clinical or differential diagnostic role (Fig. 8.1.1) [1, 2, 10].
8.1.1.2 Etiopathology of the Cutaneous Symptoms

To date, no single pathway can explain the photosensitization evoked by porphyrins and UV-light. Still, a number of cellular and soluble factors are known to be potentially involved, among them are reactive oxygen species, particular cells (e.g., erythrocytes, mast cells, polymorphonuclear cells, and fibroblasts), and soluble mediators (e.g., the complement system, factor XII-dependent pathways, and the eicosanoids) as well as matrix metalloproteinases [2]. It is likely that interactions between these factors play an important role in the pathogenesis of the cutaneous lesions.

Porphyrins such as uroporphyrin, coproporphyrin, and protoporphyrin absorb light intensely in their Soret bands (major absorption peak between 400 and 410 nm). Absorption of this radiant energy results in the generation of excited state molecules. Excited porphyrins in their singlet and triplet states can also transfer their absorbed energy to oxygen molecules, thereby creating reactive oxygen species. Cellular and tissue damage induced by photo-activated porphyrins is believed to primarily result from the formation of reactive singlet oxygen and free radicals, with subsequent lipid peroxidation and protein cross-linking [11, 12]. The type of cellular damage depends on the solubility and tissue distribution of the porphyrins. Accumulations of water-soluble uro-, copro-, and protoporphyrin leads to blistering as seen in most of the cutaneous porphyrias, e.g., PCT, VP, and HCP. By contrast, accumulation of lipophilic protoporphyrin leads to an immediate cutaneous burning sensation after UV-light exposure, accompanied by erythema and edema as seen in EPP [12].

8.1.1.3 Etiopathology of the Acute Porphyric Attack

Two porphyria variants, AIP and δ-aminolevulinic acid dehydratase deficiency porphyria, do not manifest with cutaneous symptoms. In these porphyrias, the dysfunctional enzymes act early in heme biosynthesis and their substrates are nonphototoxic porphyrin precursors (Fig. 8.1.1). However, both AIP and δ-aminolevulinic acid dehydratase deficiency porphyria as well as VP and HCP can manifest with life-threatening acute neurological attacks. Although the exact pathogenesis of these attacks is not well understood it seems that the porphyrin precursors, δ-aminolevulinic acid (ALA) and porphobilinogen (PBG), which are massively excreted from the liver during an acute attack, are extremely neurotoxic. Thus, the autonomic and peripheral nervous systems, which do not have an appropriate barrier protection, are particularly susceptible to their action [3].

8.1.2 Clinical Characteristics and Diagnosis

8.1.2.1 Classification

Traditionally, these disorders have been subdivided into erythropoietic and hepatic forms, according to the major site of organ expression of the specific enzymatic deficiency. From a dermatologist’s perspective, the porphyrias can be classified into cutaneous and noncutaneous forms (Table 8.1.2). However, from a general clinician’s point of view it seems more suitable to classify the porphyrias into acute and nonacute forms, thereby primarily considering the occurrence or absence of potentially life-threatening acute neurological attacks (Table 8.1.3) [2, 13]. We will adhere to the latter classification throughout this chapter.

<table>
<thead>
<tr>
<th>Cutaneous porphyrias</th>
<th>Noncutaneous porphyrias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porphyria cutanea tarda</td>
<td>Acute intermittent porphyria</td>
</tr>
<tr>
<td>Variegate porphyria</td>
<td>δ-aminolevulinic acid dehydratase deficiency porphyria</td>
</tr>
<tr>
<td>Erythropoietic protoporphoria</td>
<td></td>
</tr>
<tr>
<td>Hereditary coproporphyria</td>
<td></td>
</tr>
<tr>
<td>Congenital erythropoietic porphyria</td>
<td></td>
</tr>
<tr>
<td>Hepatoerythropoietic porphyria</td>
<td></td>
</tr>
</tbody>
</table>
8.1 The Porphyrias

8.1.2.2 Clinic of the Nonacute Porphyrias

The nonacute porphyrias comprise PCT, EPP, CEP, and HEP. These porphyrias are of particular interest for dermatologists because they all primarily manifest with cutaneous symptoms (Tables 8.1.2 and 8.1.3) [1, 2].

**8.1.2.2.1 Porphyria Cutanea Tarda**

The cutaneous manifestations include increased photosensitivity and skin fragility as well as blistering, erosions, crusts, miliae, and scars on the sun-exposed areas of the body (Table 8.1.3) (Fig. 8.1.2a, b).

**Table 8.1.3** Classification of the porphyrias into acute and nonacute forms, highlighting important clinical and epidemiological aspects at a glance

<table>
<thead>
<tr>
<th>Porphyrias</th>
<th>Incidence</th>
<th>Age of onset</th>
<th>Important aspects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute porphyrias</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute intermittent porphyria</td>
<td>0.5–1 per 100.000</td>
<td>Second to fourth decade of life; very rarely before puberty</td>
<td>Most common acute porphyria in the world; acute neurological attacks but no photosensitivity/ cutaneous symptoms</td>
</tr>
<tr>
<td>Variegate porphyria</td>
<td>~1 per 300 in South Africa; relatively rare elsewhere</td>
<td>Second to third decade of life; usually not before puberty</td>
<td>Skin symptoms similar to porphyria cutanea tarda and acute attacks similar to acute intermittent porphyria can occur (neurocutaneous porphyria); founder mutations identified in South Africa and Chile</td>
</tr>
<tr>
<td>Hereditary Coproporphyria</td>
<td>Very rare (&lt;50 cases reported)</td>
<td>Usually not before puberty</td>
<td>Acute attacks similar to acute intermittent porphyria and cutaneous symptoms including erythema and blistering can occur (neurocutaneous porphyria)</td>
</tr>
<tr>
<td>ALAD deficiency porphyria</td>
<td>Extremely rare (&lt;10 cases reported)</td>
<td>Early and late onset have been described</td>
<td>Neurological symptoms similar to acute intermittent porphyria can occur; no photosensitivity/ cutaneous symptoms</td>
</tr>
<tr>
<td>Nonacute porphyrias</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
<td>Most common porphyria worldwide</td>
<td>Third to fourth decade of life; usually not before puberty</td>
<td>Most frequent type of porphyria worldwide; acquired and hereditary variants exist; moderate to severe photosensitivity; cutaneous symptoms include vesicles and bullae, erosions, crusts, miliae, scarring, hyperpigmentation, and hypertrichosis; undistinguishable from variegate porphyria</td>
</tr>
<tr>
<td>Erythropoietic protoporphryia</td>
<td>Second-highest incidence of the cutaneous porphyrias</td>
<td>Early childhood (1–4 years); late onset extremely rare</td>
<td>Cutaneous symptoms include erythema, edema, purpura, skin thickening, waxy scars; usually no blistering; in approximately 5% of the cases severe liver disease can occur</td>
</tr>
<tr>
<td>Congenital erythropoietic porphyria</td>
<td>Very rare (~150 cases reported)</td>
<td>Infancy/first decade of life</td>
<td>Very severe clinical course; vesicles and bullae, erosions, excoriations, exulceration, crusts, miliae, scarring, hyperpigmentation, and hypertrichosis; mutilation; hemolytic anemia; hepatosplenomegaly; porphyrin deposition in bones and teeth (erythrodontia)</td>
</tr>
<tr>
<td>Hepatoerythropoietic porphyria</td>
<td>Extremely rare (~25 cases reported)</td>
<td>Early infancy</td>
<td>Recessive variant of porphyria cutanea tarda; reported in the USA and Europe; markedly increased photosensitivity and severe clinical course possible; vesicles and bullae, erosions, excoriations, crusts, miliae, scarring, and hypertrichosis; mutilation can occur</td>
</tr>
</tbody>
</table>
Additionally, postinflammatory hyperpigmentation, hypertrichosis, scleroderma-like alterations, and scarring alopecia can be observed [1, 2].

A wide range of triggering factors has been reported to precipitate the clinical manifestation of PCT, among them are alcohol, estrogens, polychlorinated hydrocarbons, hemodialysis in patients with renal failure, iron, inheritance of specific mutations (C282Y and H63D) in the \( \text{HFE} \) gene underlying classic hemochromatosis, and viral infections such as hepatitis C and HIV [1, 2]. Interestingly, homozygosity for \( \text{HFE} \) gene mutation C282Y was found to be associated with an earlier onset of cutaneous lesions in both sporadic and familial PCT, the effect being more marked in familial PCT [14]. Further, PCT patients seem to have a higher risk for the development of hepatocellular carcinoma [1, 2].

### 8.1.2.2.2 Erythropoietic Protoporphyria

Clinically, EPP is characterized by cutaneous photosensitivity manifesting early in life. Acute photosensitivity episodes include burning, stinging, and pruritus in sun-exposed skin, particularly on the nose, cheeks, and dorsal aspects of the hands, followed by erythema, edema, and wax-like scarring (Table 8.1.3; Fig. 8.1.3a, b). Skin symptoms can occur within minutes of sun exposure, often starting early in spring, continuing through the summer, and diminishing in fall and winter [1, 2, 15].

A serious complication and a major concern in EPP patients is the development of cholestasis with rapid accumulation of protoporphyrin in hepatobiliary structures resulting in severe liver damage. Although rarely occurring, progressive liver failure is a well-recognized complication in EPP [16]. Unfortunately, the development of protoporphyrin-induced hepatic disease and the molecular mechanisms underlying the phenotype with severe liver injury are not well understood and it seems that other, as yet unidentified, factors may contribute to the pathogenesis of severe liver failure in EPP.

### 8.1.2.2.3 Congenital Erythropoietic Porphyria

CEP manifests shortly after birth with severe cutaneous photosensitivity, blistering, erosions, excoriations, and ulcerations followed by extensive scarring.
8.1 The Porphyrias

and deformation, mainly of the hands. In the face, loss of eyebrows and eye-lashes as well as severe mutilation involving cartilage structures, e.g., the nose, is frequently observed (Fig. 8.1.4). Further, erythropoietic protoporphyria. Acute photosensitivity reaction with unsharply demarcated erythema and edema on both hands and the wrists of a young boy.

Fig. 8.1.3 (a) Porphyria cutanea tarda. Back of the hand: Note the intact blister on the basis of digitus II as well as erosions, crusts, and miliae. (b) Porphyria cutanea tarda. Detailed view of the dorsal aspect of digitus II and III of the hand: Intact, partially, hemorrhagic blisters, erosions, crusts, and scarring.

Fig. 8.1.4 (a) Erythropoietic protoporphyria. Erythema, post-inflammatory hyperpigmentation, erosions, crusts in the face of a young girl. Note the subtle scarring on the nose. (b) Erythropoietic protoporphyria. Acute photosensitivity reaction with unsharply demarcated erythema and edema on both hands and the wrists of a young boy.
ranging from mild forms of hemolytic anemia to intra-uterine hydrops fetalis and hepatosplenomegaly are common clinical features (Table 8.1.3) [1, 2, 7].

8.1.2.4 Hepatoerythropoietic Porphyria

Clinically, HEP usually manifests in early childhood, with dark urine in the diapers being the most frequently observed first sign. Subsequently, severe cutaneous photosensitivity develops, associated with blistering, pruritus, hypertrichosis, hyperpigmentation, and scleroderma-like scarring (Table 8.1.3). If the clinical course is severe, the symptoms closely resemble those observed in CEP. However, unlike CEP, HEP is usually not associated with hematological abnormalities as, e.g., severe anemia [2, 8].

8.1.2.3 Clinic of the Acute Porphyrias

The acute porphyrias comprise AIP, VP, HCP, and δ-aminolevulinic acid dehydratase (ALAD) deficiency porphyria, (Tables 8.1.2 and 8.1.3) [2, 13].

Independent of the prevailing specific type, all patients affected by any one of the acute porphyrias can manifest a broad range of clinical symptoms that usually do not occur before puberty. An exception to this rule is the very rare ALAD deficiency porphyria in which acute porphyric attacks may manifest already in childhood [1, 10]. The symptoms include long-lasting colicky abdominal pain, nausea and vomiting, constipation, tachycardia, hypertension, seizures, muscle weakness, paraplegia and tetraplegia as well as a variety of other neurological and psychiatric signs (Table 8.1.5). This spectrum of mostly unspecific clinical signs can mimic other diseases and demands all diagnostic abilities of the attending physician because the porphyrias are rarely considered as differential diagnosis if the neurological symptoms prevail [2, 13, 17].

Acute attacks can be precipitated by a variety of factors, including porphyrinogenic drugs, alcohol, hormonal changes, recurrent or chronic infection, and reduced caloric intake due to fasting or diets [1–3, 13].

Apart from the aforementioned neurological findings, individuals suffering from VP or HCP can also manifest cutaneous symptoms on the sun-exposed areas of the skin that cannot be distinguished clinically from those encountered in PCT (Fig. 8.1.5). Therefore, VP and HCP are also referred to as neurocutaneous porphyrias. By contrast, however, AIP and ALAD deficiency porphyria do not manifest with cutaneous symptoms [1, 2, 13].

In an effort to set forth standards in diagnosis and management of the acute porphyrias and to provide information and guidelines for patients as well as physicians, an European consortium of expert porphyria specialists from different European porphyria centers has recently established the European Porphyria Foundation (EPI). On the EPI web-page (http://www.porphyria-europe.org/) that is permanently up-dated, important information on the porphyrias is available, most importantly, including a comprehensive and clearly structured guide on the usage of safe and potentially unsafe drugs in the acute porphyrias and the
8.1 The Porphyrias

contact details of the respective porphyrria centers in different European countries.

8.1.2.4 Diagnostic Tests

The diagnostic procedures involved in making a precise diagnosis of the prevailing type of porphyrria can comprise up to four important sequential steps:

- A thorough anamnesis including the family history and a physical examination regarding cutaneous symptoms on the sun-exposed body sites
- Biochemical measurement of porphyrins and porphyrin precursors in urine, feces, blood, and plasma (Table 8.1.4)
- Determination of specific enzyme activities, which is only performed in specialized laboratories upon specific indication
- Mutation analysis using molecular genetic techniques, likewise possible only in specialized laboratories [2, 13]

The porphyrias are of particular dermatologic interest because most forms manifest distinct cutaneous symptoms allowing a presumptive diagnosis based exclusively on clinical signs. Following this, specific biochemical and enzymatic tests can confirm a clinically suspected diagnosis. Today, the genetic defects underlying the porphyrias are well-characterized (Table 8.1.1), thereby also providing the possibility of molecular diagnosis and genetic counseling for affected families [2, 13]. Of note though, biochemical analysis of urine, stool, blood, and plasma samples is usually sufficient to confirm a diagnosis of porphyrria and the characteristic biochemical findings of each type of porphyrria are described at a glance in Table 8.1.4 [1, 2].

Difficulties in obtaining a correct diagnosis are primarily due to the fact that the different types of porphyrias often reveal overlapping findings with regard to clinical and/or biochemical features (for a diagnostic algorithm see Fig. 8.1.6). This is especially true for variegate porphyria that might present with cutaneous lesions similar to those observed in PCT and neurovisceral symptoms resembling those encountered in AIP. These symptoms can sometimes even manifest simultaneously in affected patients [2, 9].

![Variegate porphyria](image)

Fig. 8.1.6 Variegate porphyria. Intact blister, erosions, crusts, milia, and hyperpigmented scarring on the back of the hands. Clinically, the cutaneous lesions cannot be distinguished from those encountered in porphyria cutanea tarda

Regarding biochemical analyses, drastically elevated urinary levels of the porphyrin precursors ALA and PBG can be found during an acute attack. However, asymptomatic mutation carriers (so called “silent” carriers) are rarely detected by measurement of urinary porphyrin precursors because they often display a high variability and might be just slightly elevated or even normal in the phase between acute attacks. Thus, these methods as well as the measurement of enzymatic activities in fibroblasts or lymphocytes are somewhat imprecise, since a certain overlap between the values measured in patients, clinically unaffected “silent” carriers, and normal control individuals could be found, and the results of these analyzes were not always conclusive[18].

Therefore, the establishment of molecular genetic laboratory techniques on the basis of direct DNA analysis has been an important contribution to the traditional diagnostic procedures used in differentiation of the porphyrias [4]. Routine application of these techniques is not only important for clinicians in obtaining the most precise confirmation of a presumptive diagnosis but has also enabled researchers to learn more about the role of genes and gene products in the pathogenesis of the porphyrias. Further, affected individuals and their family can be provided with genetic counseling [2, 3, 13].

Of note, porphyrin abnormalities are also observed in lead poisoning, sideroblastic and hemolytic anemia, iron deficiency, renal failure, cholestasis, liver disease, and gastrointestinal haemorrhage. However, associated photosensitivity has only been documented in rare cases of sideroblastic anemia [2].
<table>
<thead>
<tr>
<th>Porphyria variant</th>
<th>Urine</th>
<th>Feces</th>
<th>Erythrocytes</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALA</td>
<td>PBG</td>
<td>URO</td>
<td>COPRO</td>
</tr>
<tr>
<td>Acute porphyrias</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute intermittent porphyria</td>
<td>++ to +++</td>
<td>++ to +++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Variegate porphyria</td>
<td>++ to +++</td>
<td>++ to +++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Hereditary coproporphyria</td>
<td>N to ++</td>
<td>N to ++</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td>ALD-D deficiency porphyria</td>
<td>+++</td>
<td>N</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Nonacute porphyrias</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
<td>N</td>
<td>N</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>Erythropoietic protoporphyria</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Congenital erythropoi- etic porphyria</td>
<td>N</td>
<td>N</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>Hepatoerythropoietic porphyria</td>
<td>N</td>
<td>N</td>
<td>+++</td>
<td>ISOCOPRO</td>
</tr>
</tbody>
</table>

ALA = δ-aminolevulinic acid; COPRO = coproporphyrin; N = normal; + = above normal range; ++ = slightly elevated; +++ = highly elevated; ++++ = very highly elevated; ISOCOPRO = isocoproporphyrin; PBG = porphobilinogen; PROTO = protoporphyrin; URO = uroporphyrin
8.1.3 General Therapeutic Outline

Since the porphyrias are hereditary disorders that are due to a specific genetic defect with subsequent catalytic deficiency of the encoded protein, a causal therapy could only consist of either enzyme replacement strategies or gene therapy. However, none of these therapeutic modalities are currently available for humans.

In the cutaneous porphyrias, avoidance of UV-light exposure, sun-protective clothing, and regular application of topical sunscreens is crucial, both prophylactically and therapeutically. In the acute porphyrias, identification and avoidance of porphyrinogenic drugs and other well-established factors that can provoke acute porphyrific attacks is the most important prophylactic measure that should precede all therapeutic procedures [1, 2, 13].

8.1.4 Current Established Therapies

8.1.4.1 Therapy of the Nonacute Porphyrias

In PCT, triggering factors, as e.g., alcohol ingestion and estrogen therapy should be stopped. Successful treatment can be achieved by repeated phlebotomy (venesection) of approximately 500 mL blood every 2 weeks. Some authors recommend weekly venesections of 300 mL blood. Phlebotomy usually leads to resolution of skin fragility and blistering within 2–4 months. However, normalization of urinary porphyrin concentrations will usually take longer (about 12 months). Chloroquine is thought to work by accelerating the secretion of porphyrins and may also inhibit porphyrin synthesis thereby reducing photosensitivity. The standard therapy consists of 125 mg chloroquine twice weekly and complete remission can be expected within 6–9 months (Table 8.1.5). Chloroquine and phlebotomy can be used in combination to induce faster remission [1, 2, 5]. Of note, a recent report indicates that the genetic background of PCT patients with regard to the presence of HFE gene mutations plays a critical role in the outcome of chloroquine treatment. Whereas heterozygosity for mutation C282Y and compound heterozygosity of HFE mutations did not compromise the therapeutic response to chloroquine, PCT patients homozygous for C282Y seem to retain high serum iron, ferritin, and transferring saturation and, most importantly, failed to respond to chloroquine therapy [19].

In EPP, β-carotene has proven to minimize burning, stinging and photosensitivity reactions in approximately 60% of the patients. Although it has no effect on protoporphyrin levels in erythrocytes, it reduces photosensitivity through quenching the formation of free radicals during the cutaneous photoreaction. β-carotene should be administered preferably from February to October with a pause between November to January. The doses administered range from 30 to 90 mg/day in children and 60 to 180 mg/day in adults with desirable maximum plasma levels of approximately 600–800 μg/dL. Single reports exist on therapeutic attempts with cysteine or narrow-band UVB-photoraphy, but the usefulness of these treatment modalities has so far not been convincingly demonstrated [1, 2, 15].

In CEP, surveillance of anemia and skin infections is crucial. Frequent blood transfusions can suppress
erythropoiesis thereby decreasing porphyrin production and photosensitivity. Concomitant administration of deferoxamine can reduce the resulting iron-overload. If successful, bone marrow transplantation leads to marked reduction of porphyrin levels and photosensitivity and has been reported to be curative [2, 3, 15].

Besides thorough photoprotection, no specific treatment options are currently available for HEP.

8.1.4.2 Therapy of the Acute Porphyrias

8.1.4.2.1 Therapy of the Cutaneous Symptoms

In both VP and HCP, avoidance of UV-light exposure, sun-protective clothing, and regular application of topical sunscreens is mandatory. In contrast to PCT, phlebotomy seems to be of no benefit. Although it is conceivable that antimalarials such as chloroquine might be helpful in decreasing photosensitivity in VP and HCP, also, chloroquine and its derivatives belong to the group of porphyrinogenic drugs known as potential inducers of acute porphyric attacks. Thus, the use of chloroquine in the treatment of cutaneous symptoms in VP or HCP cannot be recommended [2, 9].

8.1.4.2.2 Therapy of an Acute Porphyric Attack

An acute attack is a potentially life-threatening event with a significant mortality of up to 5% that requires rapid therapeutic intervention to prevent complications as paralysis, respiratory failure, coma, and death. Treatment should comprise the following consecutive measures (Table 8.1.6) [2, 13]:

1. Precipitating factors, e.g., porphyrinogenic drugs, must be identified and their administration should be ceased. If necessary, patients should be initially monitored in an intensive care unit.
2. Regularly encountered neurological symptoms like abdominal pain, nausea and vomiting should be treated symptomatically by, e.g., administration of pethidine or opiates and promazine/chlorpromazine, respectively.
3. The most important therapeutic step is the early intravenous administration of hemin preparations such as heme arginate (Normosang®; only available in Europe from Orphan Europe) or hematin (Panhematin®; only available in the USA from Ovation Pharmaceuticals).

In the past, acute attacks were mainly treated with glucose infusions. Due to the availability of the aforementioned hemin preparations, however, this should nowadays rather be historic than state-of-the-art treatment. Thus, glucose should only be administered as an adjuvant, if at all. If heme preparations are not immediately available, glucose infusions may be given to bridge the time span until hem arginate or hematin can be administered.

Since the early 1970s, acute attacks were treated with hematin preparations [20]. These preparations had the disadvantage of being very unstable. Further, thrombophlebitis as an adverse effect was reported in a high percentage of patients treated [21, 22]. Heme arginate is composed of human hemin and L-arginine as an additive to increase solubility and stability of the product. In contrast to the older hematin preparations, heme arginate does not induce any significant changes in coagulation and fibrinolysis and the frequency of thrombophlebitis as well as the overall rate of side effects is markedly reduced [8, 23]. Heme arginate is administered as a short-time infusion (15–20 min) in a dosage of 3 mg/kg bodyweight/day on four consecutive days.

8.1.5 Experimental Approaches

Of the following treatment modalities, bone marrow and liver transplantation have certainly already passed the stage of being merely “experimental” approaches. Still, by no means they can be referred to as “routine” therapies either, in particular because (1) they are available only in specialized centers and (2) not all facets of their mode of action in the porphyrias are fully elucidated yet. Therefore, both therapeutic regimens and their sequential combination are presented within this section.

8.1.5.1 Bone Marrow Transplantation

Over the last years, bone marrow transplantation has been repeatedly used in the treatment of, e.g., CEP [7, 24–27] and EPP [28, 29], although with varying success. This promising therapeutic regimen harbors major complications such as, e.g., graft rejection, graft-vs-host disease, infection, sepsis, and death. Due
### 8.1 The Porphyrias

#### Table 8.1.6 Therapy of the acute and nonacute porphyrias at a glance

<table>
<thead>
<tr>
<th>Porphyrias</th>
<th>Therapy strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute porphyrias</strong></td>
<td></td>
</tr>
<tr>
<td>Acute intermittent porphyria; variegate porphyria; hereditary coproporphyria; ALA-D deficiency porphyria</td>
<td>Acute attacks&lt;br&gt;Identification and elimination of precipitating factors (porphyrinogenic drugs; alcohol; hormones)&lt;br&gt;Monitoring in intensive care unit and/or contact one of the porphyria centers&lt;br&gt;Adequate pain therapy, e.g., with pethidine or other opioid derivatives&lt;br&gt;Adequate therapy of nausea and vomiting, e.g., with promazine, chlorpromazine or triflupromazine&lt;br&gt;Intravenous administration of either heme arginate (Normosang®; Europe only) in a dosage of 3 mg/kg body weight once a day as short-time infusion over 4 consecutive days or hematin (Panhematin®; USA only)&lt;br&gt;If necessary, intravenous carbohydrate substitution with glucose infusions&lt;br&gt;Laboratory control of urinary porphyrin excretion during the acute attack (daily, if possible)&lt;br&gt;<em><strong>Cutaneous symptoms (variegate porphyria; hereditary coproporphyria)</strong></em>&lt;br&gt;Photoprotection, e.g., with broad-band sunscreens and/or protective clothing&lt;br&gt;Avoidance of sunlight exposure and trauma</td>
</tr>
<tr>
<td><strong>Nonacute porphyrias</strong></td>
<td></td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
<td>Photoprotection, e.g., with broad-band sunscreens and/or protective clothing&lt;br&gt;Avoidance of sunlight exposure and trauma&lt;br&gt;Cease alcohol ingestion; stop estrogen therapy&lt;br&gt;Phlebotomy (venesection): 400–500 mL every 2 weeks over ~3–6 months&lt;br&gt;Low-dose chloroquine treatment: 125 mg twice weekly (e.g., on Monday and Thursday) over 6–12 months, until porphyrin excretion is within normal range&lt;br&gt;Laboratory control of urinary porphyrin excretion for monitoring therapeutic outcome</td>
</tr>
<tr>
<td>Erythropoietic protoporphyria</td>
<td>Photoprotection, e.g., with broad-band sunscreens and/or protective clothing&lt;br&gt;Avoidance of sunlight exposure (common window glass does not provide protection)&lt;br&gt;Oral β-carotene: 30–90 mg/day in children; 60–180 mg/day in adults.&lt;br&gt;Desirable maximum plasma level: 600–800 μg/dL. Administration from February to October; pause from November to January</td>
</tr>
<tr>
<td>Congenital erythropoietic porphyria</td>
<td>Photoprotection, e.g., with broad-band sunscreens and/or protective clothing&lt;br&gt;Strict avoidance of sunlight exposure&lt;br&gt;Change day-night-rhythm&lt;br&gt;Splenectomy (reduces hemolysis and platelet consumption)&lt;br&gt;Bone marrow transplantation</td>
</tr>
<tr>
<td>Hepatoerythropoietic porphyria</td>
<td>Photoprotection, e.g., with broad-band sunscreens and/or protective clothing&lt;br&gt;Strict avoidance of sunlight exposure and trauma&lt;br&gt;Change day-night-rhythm&lt;br&gt;<strong>CAUTION – therapeutic approaches used in porphyria cutanea tarda (Phlebotomy; antimalarial) are ineffective!</strong></td>
</tr>
</tbody>
</table>

While the therapeutic measures in case of an acute porphyrin attack are the same for each variant of the acute porphyrias, differentiated and individual treatment strategies are recommended for the nonacute porphyrias depending on the prevailing symptoms and the respective form of porphyria.

To increasing experience with this therapy, however, the current port-transplantation survival in porphyria patients has steadily improved. Since the early 1990s, allogeneic stem cell transplantation (from bone marrow or umbilical cord blood) has emerged as a treatment option for CEP. To date, it constitutes the only known curative therapy regimen for this disease. The first allogeneic bone marrow transplantation in CEP was reported by Kauffman and colleagues in 1991 [26]. Since then, approximately 10
patients have further been successfully treated with HLA identical stem cell transplantation, including both bone marrow transplantation and cord blood stem cell transplantation [7, 24–27]. In 2005, the first successful bone marrow transplantation in matched unrelated donors was reported [24], opening new avenues for this severe disease in which patients have a markedly reduced quality of life and life expectancy.

In EPP, the excess protoporphyrin is derived from the bone marrow which enters the circulation in erythrocytes and is excreted unaltered in the feces. Hence, bone marrow transplantation would correct the tissue primarily responsible for protoporphyrin over-production and has been frequently discussed as a possible therapy for this disease [29]. To date, its use in EPP is predominantly limited by possible associated risks. Still, there are two reports on the successful and curative use of bone marrow transplantation in EPP [28, 30]. The main controversy is if bone marrow transplantation might also be sufficient to prevent or reverse the severe liver complications observed in up to 10% of these patients. Therefore, timing of bone marrow transplantation in EPP seems a crucial factor. Ideally, transplantation should be performed before severe EPP-related liver failure occurs [29]. However, it is not possible to accurately predict the predisposition for severe liver disease to date.

### 8.1.5.2 Liver Transplantation

The successful use of liver transplantation has been reported in patients with EPP [31, 32], AIP [33], and VP [34]. Beside the problem of insufficient organ availability, the same risk factors and complications prevail as outlined for bone marrow transplantation. In the acute porphyrias, such as AIP and VP, liver transplantation might be a good therapeutic option for those patients with repeated life-threatening acute attacks, poor quality of life, requirement of respiratory support, and progressive loss of venous access due to repeated intravenous administration of hemin infusions [32].

Currently, the best-documented experience with liver transplantation is with regard to EPP. In severe advanced hepatic failure, liver transplantation is a well-established therapeutic possibility. To date, approximately 20 EPP patients have undergone liver transplantation in Europe (European Liver Transplant Registry 2008) and also approximately 20 in the USA. Although patient and graft survival are similar to other indications, most patients experience recurrence of EPP liver disease, since the excess production of protoporphyrin by the erythroid tissue remains unchanged [30].

Recently, successful liver transplantation in the acute porphyrias has been reported in four patients with AIP [33] and one with VP [34]. In three of the individuals with AIP, the urinary excretion levels of the heme precursors δ-aminolevulinic acid and PBG rapidly decreased to normal values after the transplantation. With regard to long-term follow-up, one of these patients has remained entirely free from acute porphyria attacks over a period of 4 years [33], indicating that this therapeutic intervention might be curative both biochemically and clinically.

### 8.1.5.3 Combined Liver and Bone Marrow Transplantation

There is one report on the therapeutic intervention in EPP by sequential liver and bone marrow transplantation [35]. As mentioned earlier, liver transplantation has been successfully used to treat EPP patients with severe liver failure [31, 32], but continuing excess production of protoporphyrin by the bone marrow caused recurrence of liver disease in the majority of these individuals. In a single patient, the sequential combination of both liver and bone marrow transplantation led to amelioration of the severe phenotype, resolving photosensitivity and halting EPP associated liver graft injury. Further, additional splenectomy seemed to facilitate the successful bone marrow transplantation [35].

### 8.1.5.4 Therapy with [Nle₄, D-Phe₇]-Alpha-Melanocyte Stimulating Hormone

On 08 May 2008, the European Commission granted the designation of an Orphan Medicinal product to [Nle₄, D-Phe₇]-alpha-melanocyte stimulating hormone (CUV1647; Melanotan) for the treatment of EPP
(EU designation number EU/3/08/541) and CEP (EU designation number EU/3/08/545), respectively.

Recently, a phase II clinical trial on the effectiveness of CUV1647 in the treatment of EPP has been performed in Australia and Switzerland with encouraging results. Currently, further patients with EPP are enrolled in a multicenter clinical phase III trial in several European countries and the United States to evaluate the effectiveness of this drug in a larger cohort of patients. CUV1647 stimulates the physiological production of melanin, resulting in an increased cutaneous pigmentation. This pigmentation protects the skin from ultraviolet damage. CUV1647 is delivered through a subcutaneous implant every 2 months, providing controlled release of the active drug, alpha-melanocyte stimulating hormone.

8.1.5.5 Enzyme Replacement Therapy

To date, the only type of porphyria that has been approached by enzyme replacement therapy in humans is AIP.

On 12 June 2002, orphan designation (EU/3/02/103) was granted by the European Commission for recombinant human porphobilinogen deaminase (rhPBGD) for the treatment of AIP. Administration of rhPBGD was expected to act by decreasing plasma concentration of heme precursors. At that time, the effects of rhPBGD had already been evaluated in an experimental mouse model, in which the biochemical porphyrin and porphyrin-precursor excretion patterns of acute porphyric attacks had been mimicked by phenobarbital induction of heme biosynthesis [36]. Although the initial studies in 20 asymptomatic PBGD-deficient subjects (both male and female) with ≥4 times the upper reference urinary PBG level showed that the rhPBGD enzyme preparation was safe to administer and effective for the removal of accumulated porphyrin precursor porphobilinogen from plasma and urine [37]; the subsequent evaluation, in a multicenter trial, of the effects in AIP patients with acute attacks were rather disappointing and not superior to placebo. Unfortunately, according data on the ineffectiveness of rhPBGD in the treatment of acute porphyric attacks have not yet been published and the ongoing trial was stopped without further pursuing the approach of intravenous administration of rhPBGD or even notifying those patients who had already been enrolled at that phase. The results were presented, though as an oral presentation, a few years later during the biennial international meeting on Porphyrins and Porphyrias in Rotterdam, the Netherlands, in May 2007.

8.1.5.6 Gene Therapy

An imminent goal of gene therapy approaches in both CEP and EPP is the achievement of long-term expression of the therapeutic gene in a given hematopoietic lineage. In this respect, murine models for the aforementioned types of porphyrias have been developed to facilitate the exploration of phenotype reversion in vivo [38]. The restoration of deficient enzymatic activity in the bone marrow compartment following gene therapy has been extensively studied. Murine onco-retroviral, and recently, lentiviral vectors have been successfully used to transduce hematopoietic stem cells, allowing full metabolic and phenotypic correction of both EPP and CEP mice [38–40]. In CEP, a selective survival advantage of corrected cells was demonstrated in mice [40], reinforcing the arguments for a gene therapy approach in the according human disease. Consequently, the European commission has recently approved a protocol for the application of gene therapy in selected patients with CEP.

Recently, increasing efforts have been made in developing gene therapy protocols for AIP. These approaches comprise both viral and nonviral gene delivery strategies [41]. In May 2007, the results of an extensive in vivo study on the effectiveness of gene therapy with AMT-020 for the treatment of AIP in a murine model have been presented by researchers of the Centro de Investigación Médica Aplicada (CIMA) at the University of Navarra, Pamplona, Spain, during the world conference, Porphyrins and Porphyrias in Rotterdam, the Netherlands. AMT-020 is comprised of an adeno-associated virus (AAV) vector delivering the gene for PBGD. The eventual aim of this study was to investigate the potential of AMT-020 to protect against acute porphyric attacks induced by phenobarbital in a mouse model of AIP. The model reproduces the key features of the acute attack in human AIP patients, including increased
urinary excretion of heme precursors and decreased motor function. The data presented suggest that AMT-020 has the potential to protect AIP patients suffering from acute attacks and/or neuropathy. As a consequence, a clinical phase I trial for the evaluation of the feasibility, safety, and effectiveness of AMT-020 in the treatment of AIP in humans is expected to start in the near future.

8.1.6 Complications to Avoid

Among the acute porphyrias, a small percentage of predominantly female patients with either AIP or VP manifest recurrent acute porphyric attacks that occur more than four times per year, sometimes even in intervals shorter than 1 month. These patients experience a significant decrease in quality of life because the treatment of each attack usually requires hospitalization for several days. With increasing frequency of such attacks, management of these individuals becomes more difficult since from a given moment, peripheral venous access is impossible and even the relatively safe procedure of intravenous administration of heme preparations via a Port-a-Cath® system becomes difficult over time due to complications such as infection, occlusion, thrombosis, and extravasation.

Take Home Messages

- Establishing the diagnosis of porphyria can be difficult because the different types often reveal uncharacteristic clinical symptoms and overlapping biochemical findings. These difficulties are most obvious in VP and HCP where cutaneous lesions appear similar to those found in PCT and neurological symptoms mimicking many other diseases and particularly those encountered in the most common type of acute porphyria, AIP.
- The biggest challenge with regard to biochemical analyses is the identification of clinically asymptomatic mutation carriers, in particular children before puberty. These so-called “silent carriers” are only rarely detected by the traditional measurement of urinary and/or fecal porphyrins and porphyrin precursors which often display a high variability. These biochemical methods and the measurement of enzymatic activities in fibroblasts or lymphocytes are somewhat imprecise since a certain overlap between the values measured in patients, clinically unaffected silent carriers, and normal control individuals can be found.
- However, the recent progress in the field of molecular genetics has provided clinicians and medical researchers with permanently advancing molecular biological techniques and novel insights into the complexity of genetic disorders. Today, these modern genetic techniques enable us to transfer our clinical observations and biochemical data to the laboratory bench for diagnostic complementation by PCR-based DNA testing. Understanding the molecular basis of the porphyrias is essential for genetic engineering and the development of gene therapy strategies that will not only serve those suffering from porphyria but eventually also benefit patients with different genetic disorders. The advancing progress in basic science has made an invaluable contribution to the rapid translation of discoveries made today in the laboratory into new diagnostics and therapeutics in the near future.

References


8.2.1 Amyloidosis

Key Features

- The clinical signs are heterogeneous.
- Alkaline Congo red, methyl violet, and thionflavin-T are useful histological stainings for the diagnosis.
- Standard therapies of AL amyloidosis in the 1990s include oral melphalan and prednisone, and high-dose melphalan followed by autologous stem cell transplantation.
- Topical and intralesional steroid, dimethyl sulphoxide (DMSO), tacrolimus, laser, and dermablasion have been reported as therapies of cutaneous amyloidosis.
- New therapeutic approaches of AL amyloidosis include lenalidomide in combination with dexamethasone.

8.2.1.1 Etiology and Pathophysiology

Amyloid fibrils have been shown as the generic term of proteins, which have a beta-pleated sheet configuration. Amyloidosis is a heterogeneous disease, characterized by the deposits of a group of unrelated precursor proteins, in which normally soluble amyloid fibrils are deposited in the extracellular space in an insoluble fibrillar form caused by abnormal metabolism. The biological composition of amyloid fibrils varies according to the clinicopathophysiologic type of amyloidosis (Table 8.2.1).

8.2.1.2 Clinical Characteristics and Diagnosis

The skin signs of AL amyloidosis (primary and myeloma-associated systemic amyloidosis) are heterogeneous consisting of purpura, hyperpigmentation, waxy papules, nodules, bullae, and sclerodermatous infiltration. Other extracutaneous features may include heart and renal failure, carpal tunnel syndrome, and gastrointestinal tract involvement with hemorrhage and diarrhea. The amyloid deposits undergoing long-term hemodialysis mainly occur in bone and arthrogenous. Skin signs may include papules, nodules, and hyperpigmentation. Although skin involvement in secondary systemic amyloidosis associated with chronic inflammatory conditions is rare, amyloid infiltrations in liver and kidney are often found. Familial amyloid polyneuropathy is autosomal dominant disorder caused by mutations in the transthyretin gene. Aberrant transthyretin protein is accumulated in peripheral nerve. Sensory disturbance, dyshidrosis, skin atrophy, and ulcer may occur due to amyloid deposits in small vessels, nerves, and sweat glands. Localized cutaneous amyloidosis is mainly classified into a primary phenomenon, such as lichen, macular and nodular localized cutaneous amyloidosis, and a secondary phenomenon associated with another cutaneous pathology. Lichen amyloidosis is a persistent pruritic eruption of multiple discrete hyperkeratotic papules on the shins. Macular amyloidosis is a pruritic eruption of small brownish macules distributed...
Table 8.2.1 Classification of amyloidosis

<table>
<thead>
<tr>
<th>Type</th>
<th>Precursor protein</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systemic amyloidosis</strong></td>
<td></td>
</tr>
<tr>
<td>AL amyloidosis</td>
<td>( \lambda ) or ( \kappa ) immunoglobulin light chains</td>
</tr>
<tr>
<td>Secondary systemic amyloidosis</td>
<td>Serum amyloid A protein</td>
</tr>
<tr>
<td>Familial amyloid polyneuropathy</td>
<td>Transthyretin</td>
</tr>
<tr>
<td>Hemodialysis-related amyloidosis</td>
<td>( \beta_2 )-microglobulin</td>
</tr>
<tr>
<td><strong>Localized cutaneous amyloidosis</strong></td>
<td></td>
</tr>
<tr>
<td>Lichen amyloidosis</td>
<td>Keratin?</td>
</tr>
<tr>
<td>Macular amyloidosis</td>
<td>Keratin?</td>
</tr>
<tr>
<td>Nodular localized cutaneous amyloidosis</td>
<td>( \lambda ) immunoglobulin light chain</td>
</tr>
</tbody>
</table>

Fig. 8.2.1 Reddish nodule on the left cheek in a patient with nodular localized cutaneous amyloidosis

- Typically in a rippled, symmetrical fashion on the upper back. Nodular localized cutaneous amyloidosis commonly presents multiple lesions on the face, trunk or lower limbs (Fig. 8.2.1). Recently, missense mutations in the OSMR gene, encoding oncostatin M-specific receptor b, were identified in a large Brazilian family with familial primary localized cutaneous amyloidosis [1]. The definite diagnosis makes due the proof of amyloid deposits in skin, rectal or gastric biopsy. Skin biopsy reveals eosinophilic homogeneous deposits in the dermis. Amyloid staining includes alkaline Congo red under polarizing light, giving apple-green birefringence, and methyl violet, thioflavin-T (Fig. 8.2.2).

8.2.1.3 General Therapeutic Outline

The treatment of systemic amyloidosis is directed both toward the affected organ and to the specific type of the disease. Standard treatments of AL amyloidosis in the 1990s included oral melphalan plus prednisone, and high-dose melphalan followed by autologous stem cell transplantation. A recent randomized trial has shown that high-dose melphalan followed by autologous stem cell transplantation is not superior to standard melphalan plus dexamethasone [2]. However, there was still insufficient evidence and the result must be interpreted with caution. The combination of the protease inhibitor bortezomib and dexamethasone has also been reported to be feasible in patients with AL amyloidosis [3]. Topical and intralesional steroid are useful for cutaneous amyloidosis. However, none of the local treatments totally eradicates lesions, which can recur later.

8.2.1.4 Current Established Therapies

Lenalidomide is an immunomodulatory drug, structurally related to thalidomide, with pleiotropic activity including antiangiogenic and antineoplastic properties. Lenalidomide in combination with dexamethasone currently has become the new remarkable treatment of choice in AL amyloidosis, which is the most effective in multiple myeloma who are not candidates for high-dose therapy [4, 5]. Successful treatment with oral DMSO and 0.1% topical tacrolimus was reported in several cases of lichen amyloidosis [6, 7]. Several surgical procedures such as dermablation and laser treatment were described in cases of cutaneous amyloidosis [8, 9].

8.2.1.5 Complications to Avoid

Cardiac and renal failures in AL amyloidosis are severe complications leading to the major causes of death. Nodular localized cutaneous amyloidosis rarely

Take Home Message

- The prognosis of AL amyloidosis is still poor. Further development of novel therapeutic approaches may improve the survival rate of the disease.
develops multiple myeloma later. Therefore careful follow-ups are needed.

### 8.2.1.7 Global Variations

Several trials of treatment for localized cutaneous amyloidosis have been described across the world. Etretinate or acitretin therapy has been beneficial in some European patients [7, 8]. Limited use of calcipotriol or phototherapy has been reported by authors from Southeast Asia [9, 10].

### 8.2.2 Xanthoma

#### 8.2.2.1 Etiology and Pathophysiology

Oxidized LDL has been shown to exhibit a number of potentially proatherogenic actions and properties, including scavenger receptor-mediated uptake and lipid accumulation within macrophages. Xanthoma is characterized by accumulations of lipid-phagocytic macrophages, so called foam cells. The disease can be a reflection of lipid metabolism alteration or a result of local cell dysfunction.

#### 8.2.2.2 Clinical Characteristics and Diagnosis

Xanthomas are classified broadly into two categories; xanthoma associated with or without hyperlipidemia. Xanthoma without hyperlipidemia is caused by abnormal local lipid metabolism, certain inflammatory skin disorders, and cutaneous lymphoma/histiocytosis. Furthermore, xanthomas can be clinically subdivided into tuberous xanthoma, tendinous xanthoma, xanthelasma palpebrarum, eruptive xanthoma, generalized plane xanthoma, and plane xanthoma (Table 8.2.2). Tuberous xanthoma shows firm yellow nodules on the pressure areas, such as the extensor surfaces of the knees/elbows, and buttocks. Tendinous xanthoma develops enlarged subcutaneous nodules related to the tendons of the Achilles, hands and feet. Xanthelasma

---

**Fig. 8.2.2** Congo red staining of a patient with nodular localized cutaneous amyloidosis reveals amyloid deposits in the dermis

---

### Key Features

- Xanthomas are classified into two categories; xanthoma associated with or without hyperlipidemia.
- Therapies of xanthoma with hyperlipidemia initially consist of diet and medications such as statins, fibrates, anion exchange resins, and nicotinic acid.
- Surgical resection, carbon dioxide/erbium; YAG/argon laser, and trichloroacetic acid (TCA) peeling are tolerated by patients with xanthelasma.
palpebrarum appears as symmetric soft yellowish papules on the inside of upper eyelids (Fig. 8.2.3). Eruptive xanthoma commonly arises over the buttocks and the extensor areas of the extremities. The lesions show small, red–yellow papules with itching. Eruptive xanthoma is sometimes associated with diabetes mellitus. Generalized plane xanthoma can cover large areas of the face, neck, and thorax. Secondary localized plane xanthoma is associated with photosensitive disease and cutaneous lymphoma. Skin biopsy reveals the presence of vacuolated macrophages: foam cells. Cholesterol, LDL and triglyceride in patients with xanthoma should be investigated. Lipoprotein electrophoresis can directly detect abnormal lipoprotein metabolism. Xeroradiography and soft X-ray radiography may be useful diagnostic tools for tendinous xanthoma.

However, skin lesions are often persistent with these medications. Surgical excision and laser therapy can be used for unresponsive xanthomas.

8.2.2.4 Current Established Therapies

Many treatment modalities have been described for xanthelasma palpebrarum. Surgical resection, carbon dioxide/erbium;YAG/argon laser, and TCA peeling were tolerated by patients with xanthelasma palpebrarum [10-13]. Although probucol is not approved in Europe and the United States, it is one of the important medical therapeutic options in Japan. Probucol exerts its positive effect on xanthoma regression by reducing the size of HDL particles. Regression of xanthelasma was reported in patients treated with probucol [14].

8.2.3 Fabry Disease

8.2.3.1 Etiology and Pathophysiology

Sphingolipidosis is a group of inherited lysosomal storage disorders caused by a deficiency of lysosomal enzyme, leading to excessive intra-lysosomal deposits of sphingolipids. Fabry disease belongs to a group of sphingolipidosis, characterized by angiokeratoma

---

### Table 8.2.2 Xanthoma associated with hyperlipidemia

<table>
<thead>
<tr>
<th>Hyperlipidemia</th>
<th>Xanthoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercholesterolemia (type II</td>
<td>Tuberous xanthoma,</td>
</tr>
<tr>
<td>hyperlipidemia)</td>
<td>tendinous xanthoma,</td>
</tr>
<tr>
<td></td>
<td>xanthelasma palpebrarum</td>
</tr>
<tr>
<td>Hypertriglyceridemia (type I, IV, and</td>
<td>Eruptive xanthoma</td>
</tr>
<tr>
<td>V hyperlipidemia)</td>
<td></td>
</tr>
<tr>
<td>Obstructive jaundice</td>
<td>Plane xanthoma</td>
</tr>
<tr>
<td>Monoclonal gammopathy</td>
<td>Generalized plane xanthoma</td>
</tr>
</tbody>
</table>

---

Fig. 8.2.3 Soft yellowish papules on the upper eyelids in a patient with xanthelasma palpebrarum
corporis diffusum. Angiokeratoma develops as a result of lysosomal storage in cutaneous vascular endothelial cells. Fabry disease is X-linked recessive disease caused by a deficiency of alpha-galactosidase A and resulting in an accumulation of globotriaosylceramide in the renal and cardiovascular systems, as well as in the skin.

8.2.3.2 Clinical Characteristics and Diagnosis

Angiokeratoma may occur predominantly on the scrotum, penis, thighs, and buttocks, but spread to the trunk and limbs later. Constant severe acral paresthesia may occur in childhood. Heart, renal and cerebrovascular dysfunction can often appear in adulthood. Ultrastructural examination reveals lysosomal inclusions with a concentric lamellar configuration in the vascular endothelial cells. There is evidence of a deficiency of alpha-galactosidase A activity in Fabry’s leukocytes and/or plasma.

8.2.3.3 General Therapeutic Outline

Treatment is limited symptomatic management of acral paresthesia and the complications of heart/renal failure and strokes. The prognosis of the disease is poor and few patients live to be older than 40–50 years.

8.2.3.4 Current Established Therapies

Safety recombinant alpha-galactosidase A replacement therapy improved vascular endothelial deposits of globotriaosylceramide from the skin, kidneys, and heart in patients with Fabry disease, reversing the pathogenesis of the chief clinical manifestations of this disease [15]. Two recombinant alpha-galactosidase A: agalsidase a and agalsidase b are available. Current treatment of angiokeratomas is based mainly on the use of laser systems, including Nd:YAG laser, copper vapor laser, and flashlamp-pumped dye laser [16].

8.2.3.5 Experimental Approach

The usefulness of a pharmacological chaperone for correction of the lysosomal storage in Fabry fibroblasts with residual alpha-galactosidase A activity has been described [17]. Pulmonary instillation of a recombinant adenoviral vector encoding alpha-galactosidase A into Fabry mice resulted in high-level transduction and expression of the enzyme in the lung, as well as in the plasma, liver, spleen, heart, and kidneys. Thus, several new therapeutic options for Fabry disease are now under investigation.

8.2.3.6 Global Variations

New recombinant alpha-galactosidase A replacement therapy has been found to be useful to prevent the progress of a disease. In 2001, it had been approved earliest in Europe. Subsequently, it had been approved in US and Japan. This therapy is now available worldwide.

Take Home Message

- Early diagnosis and adequate treatment by a number of specialists can extend lifespan and improve quality of life in patients with Fabry disease.

8.2.4 Calcinosis Cutis

Key Features

- Calcinosis cutis is classified into four major subtypes: metastatic, dystrophic, idiopathic and iatrogenic.
- Multiple firm whitish dermal papules, plaques and nodules, and subcutaneous nodules are clinically found on the face and extremities.
- Sodium thiosulfate, bisphosphonates, and cinacalcet are effective therapeutic options of calciphylaxis.
- Painful nodules are indications for surgical removal.
- Therapy with calcium antagonist diltiazem and electric shock wave lithotripsy (ESWL) were beneficial in some cases.
- Topical Myo-inositol hexaphosphate (InsP₆) was recently demonstrated to improve artificially provoked dystrophic calcifications in soft tissues of rat.
8.2.4.1 Etiology and Pathophysiology

Calcinosis cutis is characterized by insoluble compounds of calcium deposits within the skin due to abnormal calcium or phosphate metabolism. It is classified into four major subtypes according to etiology: metastatic, dystrophic, idiopathic and iatrogenic. Metastatic calcinosis cutis is generally associated with hypercalcemia and/or hyperphosphatemia. Chronic renal failure often leads to metastatic calcification, taking the form of either benign calcification or calciphylaxis. Dystrophic calcinosis cutis occurs under the condition of normal serum calcium and phosphate levels and is often associated with connective tissue diseases, such as systemic sclerosis, CREST syndrome and dermatomyositis. Pseudoxanthoma elasticum, Ehlers-Danlos syndrome, and certain types of skin tumor also lead to calcium deposits in skin. Idiopathic calcinosis cutis occurs in the absence of known causes of tissue damage or systemic metabolic defect. Iatrogenic calcinosis cutis arises secondary to intravenous administration of solutions containing calcium or phosphate.

8.2.4.2 Clinical Characteristics and Diagnosis

In general, multiple firm whitish dermal papules, plaques, nodules, and subcutaneous nodules are found on the face or extremities. The lesions may be sometimes accompanied by an inflammatory response, resulting in blisters and painful swellings (Fig. 8.2.4). Calciphylaxis is a life-threatening entity usually seen in patients with chronic renal failure and dialysis, and ischemic cutaneous necrosis/eschar formation. The history and evolution of the lesions depend on the etiology of the calcification. Tests of serum calcium and phosphate may be helpful. Radiographic examination may demonstrate the extent of tissue calcification (Fig. 8.2.5). Skin biopsy reveals amorphous basophilic deposits in the dermis, which is confirmed on Von Kossa staining.

8.2.4.3 General Therapeutic Outline

Painful nodules are indications for surgical removal. The underlying problem of hypercalcemia/hyperphosphatemia should be corrected. Treatment with intraleisonal corticosteroids may be beneficial [18].

8.2.4.4 Current Established Therapies

A recent review for treatment of calciphylaxis has been described that sodium thiosulfate, bisphosphonates, and cinacalcet are effective agents, although its evidence was limited to case reports [19]. Treatment with calcium antagonist diltiazem is effective in some cases of calcinosis with CREST syndrome and dermatomyositis [20, 21]. ESWL was successful in one case of calcinosis cutis with dermatomyositis [22].

8.2.4.5 Experimental Approaches

InsP₆ is known to exhibit an extraordinary capacity as a crystallization inhibitor of calcium salts. Topical InsP₆ was recently demonstrated to improve artificially provoked dystrophic calcifications in soft tissues of rat [23]. Expression of osteopontin, which is a regulator of osseous and extra-osseous calcification processes, is upregulated in vascular endothelial cells and fibrobrasts from patients with systemic sclerosis with calcinosis, compared to those without calcinosis, by immunohistochemistry analysis [24].
8.2.4.6 Complications to Avoid

Complications of calcinosis cutis may include secondary ulceration and restrict mobility in joints. Ulceration may be complicated by bacterial infection.

8.2.5 Hemochromatosis

Key Features

- The most frequent form of hemochromatosis, HFE hemochromatosis, is caused by mutations of the \textit{HFE} gene.
- The classic triad consists of cirrhosis, cutaneous hyperpigmentation, and diabetes mellitus.
- Hemochromatosis is generally treated by phlebotomy to rid the body of excess iron.
- The capacity of desferrioxamine to chelate iron is well documented.
- Recently synthesized iron binding dendrimers reduce its absorption in the rat intestine.
- Deferiprone individually and in combination with vitamin C improved the biochemical and histological findings of myocardial damage in iron-loaded rats.

8.2.5.1 Etiology and Pathophysiology

Iron overload related to abnormal iron metabolism leads to multiple organ deposits consisting of ferritin and hemosiderin. These deposits in parenchymal cells result in cellular toxicity, tissue injury, and organ fibrosis. Cellular injury is induced by iron-generated oxyradicals and peroxidation of lipid membranes. Primary hemochromatosis is a genetic disorder, whereas secondary hemochromatosis can be the result of a variety of disorders, such as chronic hemolytic anemias, alcoholic liver injury, blood transfusion, excessive intake of iron, and porphyria cutanea tarda. Primary hemochromatosis is an autosomal recessive trait caused by iron over-absorption from intestinal tract. At least three entities (HFE hemochromatosis, juvenile hemochromatosis and transferrin receptor 2 hemochromatosis) are involved [25]. HFE hemochromatosis is the most frequent form, representing more than 90% of hemochromatosis cases. Recently, HFE hemochromatosis was mapped to 6p21.3 and mutations were identified in \textit{HFE} gene [26]. Most cases with HFE hemochromatosis have p.C282Y mutations. 0.5% of a population of white adults of northern European ancestry showed homozygous condition for this mutation [27].
8.2.5.2 Clinical Characteristics and Diagnosis

The classic triad resulting from hemochromatosis consists of cirrhosis, cutaneous hyperpigmentation, and diabetes mellitus. Other cutaneous features may include xeroderma, skin atrophy, spider angioma, and koilonychia. Skin biopsy reveals increased melanin within the epidermal basal layers. The deposits around the blood vessels and within the basement membrane zone of sweat glands stain positively with an iron staining, such as Berlin blue staining. Serum iron concentration, transferrin saturation, and serum ferritin level in patients can be elevated. An iron excretion test with deferoxamine may have diagnostic implications. Currently, the diagnosis can be confidently based on genetic testing. Liver biopsy is no longer essential for diagnosis in many cases. However, liver biopsy is still useful to determine the presence or absence of cirrhosis, which directly affects prognosis.

8.2.5.3 General Therapeutic Outline

Hemochromatosis is generally treated by phlebotomy to rid the body of excess iron.

8.2.5.4 Current Established Therapies

The capacity of desferrioxamine to chelate iron and mediate its excretion in iron overloaded patients is well documented.

8.2.5.5 Experimental Approach

Iron binding dendrimers have recently been synthesized [28]. Dendrimers terminated with hydroxypiridinone reduce its absorption in the rat intestine. The application of these dendrimers may be a novel approach for the treatment of hemochromatosis. Another experiment was demonstrated to compare the protective effect of iron chelators, desferrioxamine and deferiprone, individually and in combination with the anti-oxidant, vitamin C, in the prevention of myocardial damage in iron-loaded rats [28]. Less histopathological cardiac changes and a significant decrease in biochemical parameters were observed in rats treated with deferiprone. Moreover, additional administration of vitamin C improved the biochemical and histopathological changes in comparison to those rats administered with deferrioxamine or deferiprone individually.

8.2.5.6 Complications to Avoid

The main causes of death are hepatic failure due to cirrhosis and cirrhosis with liver cancer. Other main complications may include diabetes mellitus, congestive heart failure, and cardiac arrhythmias.

Take Home Message

- Early diagnosis and adequate therapeutic phlebotomy can prevent all known complications of hemochromatosis.

8.2.5.7 Global Variations

Recently, authors from Italy reported for the first time, a case of heart failure in the setting of unrecognized juvenile hemochromatosis successfully treated by the simultaneous administration of deferoxamine and deferiprone [29]. This will become one of the potential therapeutic options of hemochromatosis. Treatment with deferoxamine and deferiprone may gradually spread across the world.

References

495

combination of bortezomib and dexamethasone. Haematologica 92:1351–1358
9.1.1 Alopecia Areata

Key Features

- Alopecia areata is a chronic inflammatory disease characterized by nonscarring hair loss on the scalp or any hair-bearing skin and sometimes the nail deformity.
- A wide range of clinical presentations can occur, from a single patch of hair loss to complete loss of hair on the scalp (alopecia totalis) or the entire body (alopecia universalis).
- Strong direct and indirect evidence supports an autoimmune etiology for alopecia areata.
- Spontaneous remission frequently occurs in mild forms of the disease, whereas this is very unlikely in severe form.
- A number of treatments can induce hair growth in alopecia areata, but they do not cure the condition.

9.1.1.1 Etiology and Pathophysiology

It is evident that the mechanism of hair loss in alopecia areata (AA) is immunological, controlled by activated T cells (Fig 9.1.1). The model of SCID mice engrafted with patient skin strongly suggests that the hair follicle lesion is mediated by T lymphocytes [1]. There are strong indications that self-antigens, including melanocyte antigens are the key targets [2]. Associations have been reported with a variety of genes, including major histocompatibility complex, cytokine, and immunoglobulin genes [3–5]. “Immune privilege collapse model” is proposed to explain the development of autoimmunity in AA [6].
C3H/HEJ mice develop spontaneous AA-like disease, and the lesions can be transferred to uninvolved mice by grafting involved skin [7, 8]. The genetic associations in this animal model show strong linkage to chromosome 17: DQB1, DRB1, TNF, and LT and to chromosome 9: CD3 and NCAM [9]. These are clearly regions that control the immune response, and provide some idea of the genetic loci that will be identified in human AA.

9.1.1.2 Clinical Characteristics and Diagnosis

AA may start at any age and there is no known race or sex preponderance, with an estimated lifetime risk of 1.7% among the general population [10]. A wide range of clinical presentations can occur, from a single patch of hair loss to alopecia totalis (AT) or alopecia universalis (AU). The affected skin appears normal, sometimes may be slightly reddened. Short broken hairs (exclamation mark hairs) are frequently seen in expanding patches of AA. AA frequently occurs in association with atopic dermatitis and other autoimmune diseases, such as thyroiditis and vitiligo [5, 11]. The diagnosis of AA is usually not so difficult, although trichotillomania probably causes more confusion. The observation that the broken hairs are firmly anchored in the scalp unlike exclamation mark hairs is the distinguishing feature. Drug-induced anagen effluvium may mimic diffuse AA, and telogen effluvium sometimes resemble chronic stage of AT.

9.1.1.3 General Therapeutic Outline

Explanation of the clinical course and the available treatments is essential. The AA investigational assessment guideline and management guideline are helpful in establishing criteria for selecting, assessing, and treating patients [4, 12]. Leaving AA untreated is an appropriate option for many patients.

9.1.1.4 Current Established Therapies

9.1.1.4.1 Topical Corticosteroids

Potent topical corticosteroids are widely used to treat AA, but there is little evidence that they promote hair regrowth. A randomized, double-blind controlled trial with topical clobetasol propionate 0.05% showed significant effect in moderate to severe AA patients [13].

9.1.1.4.2 Intralional Corticosteroids

Intralional corticosteroids stimulate hair regrowth at the injected site in some patients. This method is suitable for treating patchy hair loss of limited extent and for the eyebrows of adult patients. Triamcinolone acetonide (5 mg/mL) is often used [5]. Intralional corticosteroids are not recommended for rapidly progressive AA or for AT/AU [4].

9.1.1.4.3 Systemic Corticosteroids

Systemic corticosteroids are effective in some patients, but their use is limited because of their side effect, high relapse rate after reduction of the dose, and the fact that steroids are necessary for long periods and do not change the ultimate prognosis [4, 5]. Thirty to forty-seven percent of patients treated with a 6-week tapering course of oral prednisolone (starting at 40 mg daily) showed hair regrowth above 25% [14].

9.1.1.4.4 Topical Immunotherapy

Topical immunotherapy is the most effective and accepted therapeutic modality in the treatment of chronic severe AA. Currently, the contact allergens used in the treatment of AA include squaric acid dibutylester (SADBE) and 2,3-diphenylcyclopropenone (DPCP). Neither SADBE nor DPCP are mutagenic [4, 5]. The patient is sensitized using a 2% DPCP in acetone applied to a small area of the scalp or 1% solution to an inside of the upper arm with patch test chamber [15]. Two weeks later the scalp is painted with DPCP, starting at 0.0001%, and this is repeated at weekly intervals. The concentration is increased at each treatment until a mild dermatitis reaction is obtained. Efficacy of DPCP in the treatment of AA has varied from study to study [16]. The success rate in achieving a cosmetically acceptable result at our hospital is approximately 60% in those patients with 25–99% scalp involvement, and 30% in AT/AU [17]. Clinically significant regrowth occurred in about 30% of patients after 6 months of treatment but this increased to 78% after 32 months of treatment [18].
The response rate of topical immunotherapy in children is about 30% (Fig. 9.1.2), but less than 10% can sustain the effect [19]. Topical immunotherapy is an unlicensed treatment that uses an experimental grade reagent. Patients should be fully informed about the nature of topical immunotherapy.

9.1.1.4.5 Minoxidil

Minoxidil is known to enhance hair growth and is widely used for androgenetic alopecia [20]. Cosmetically acceptable hair regrowth in patients with AA using topical minoxidil solution has been shown to be approximately 20–45% in patients with 20–99% scalp involvement [21, 22].

9.1.1.4.6 Dithranol (Anthralin)

Dithranol have a nonspecific immunomodulating effect eliciting hair regrowth [23, 24]. Cosmetically acceptable regrowth has been reported to vary from 20 to 25% [23].

9.1.1.4.7 Photochemotherapy

Success rates of PUVA treatment for AA are 60–65% [25–27]. The major problem with PUVA therapy is that continued treatment is necessary to maintain hair growth, leading to high cumulative UVA dose.

9.1.1.4.8 Wigs

For many patients with extensive AA wearing a wig is appropriate.

9.1.1.5 Experimental Approaches

9.1.1.5.1 Steroid Pulse Therapy

There are several reports of high-dose pulsed corticosteroid treatment for moderate to severe AA with different regimens [28–30]. One controlled study with oral regimen showed 60% effectiveness [29].

9.1.1.5.2 Ciclosporin

Ciclosporin stimulates hair regrowth in some patients with AA [31, 32]. However, side effects are a major problem.
9.1.1.5.3 Aromatherapy

One randomized double-blind trial showed a significant positive effect of aromatherapy [33].

9.1.1.5.4 Biologic Immunomodulators

So far, there are a few reports for the treatment of AA using new biologics. Etanercept and Infliximab, both block TNF-α; they appear to be ineffective in treating subjects with treatment-refractory, moderate to severe AA, AT, or AU [34–36]. On the contrary, Alefacept and Efalizumab, which inhibit T cell activation, showed significant effects for moderate and severe AA [37, 38]. Further prospective, randomized, double blind, placebo-controlled studies are necessary to evaluate the long-term efficacy and safety of biologic immunomodulators in AA.

9.1.1.6 Complications to Avoid

Folliculitis by topical corticosteroid treatment and skin atrophy by the intralesional corticosteroid are the common side effects. There is a risk of cataract if intralesional corticosteroids are used to treat eyebrows [39]. In topical immunotherapy, most patients will develop regional lymphadenopathy during the therapy [4, 5]. Severe dermatitis is the most common adverse event, and other adverse effects include urticaria and vitiligo [40, 41].

Take Home Message

- AA is not a life-threatening disease, but life-altering disease. Quality of life of patients is extremely deteriorated. We have established that AA is a T-cell mediated autoimmune disease. Treatments can induce hair growth in AA, but they do not cure the condition. New biologic immunomodulators provide hopeful strategy for the treatment of AA.

9.1.1.7 Global Variations

Thirty-four to fifty percent of patients will recover within 1 year, although most will experience more than one recurrence. Fourteen to thirty percent of patients progress to AU or AT, and full recovery from these forms is unusual (<10%) [42, 43]. Familial history of autoimmune disease, personal history of atopy, severe hair loss, onset in childhood, and nail abnormalities have been associated with a poor prognosis [44]. The prognosis is less favorable when the onset occurs during childhood [43, 45, 46]. Long-term follow-up study of AA patients suggests that severity of AA at the time of first consultation is an important prognostic factor [47].

9.1.2 Androgenetic Alopecia

9.1.2.1 Etiology and Pathophysiology

In 1942, Hamilton [48] established the pathogenic significance of androgens and genetic factors in androgenetic alopecia (AGA). The essential pathogenic
phenomenon is the shortening of anagen phase in hair cycle (Fig. 9.1.3) and subsequently the miniaturization of hair follicles. Androgens stimulate human hair growth in some sites such as the beard, axillary, and pubic areas, whereas suppress the growth of frontal scalp hair in genetically disposed individuals [49]. The expression levels of type II 5α-reductase and androgen receptor in the dermal papilla cells, mesenchymal cells of hair follicles, have been shown to correlate well to the androgen sensitivity of the hair follicles [50–54]. These findings suggest that the primary target cells in human hair follicles that respond to the action of androgen are dermal papilla cells, which mediate the signals to follicular epithelial cells in a paracrine fashion. Androgen-induced TGF-β, one of catagen inducers [55], from dermal papilla is reported to mediate this event [56]. However, many other factors involved in hair cycle regulation may play roles in AGA formation. The pathophysiology of female AGA (FAGA) is still unknown although androgens play a role in some patients responding to antiandrogen.

### 9.1.2.2 Clinical Characteristics and Diagnosis

In male AGA, vellus hair transformation occurs on the frontal and vertex scalp. Women with FAGA showed the diffuse hair thinning with preserved frontal hairline. The diagnosis of AGA and FAGA can usually be established from clinical appearance. The pattern of hair loss in AGA and FAGA is categorized by Hamilton-Norwood and Ludwig classification, respectively [57, 58]. The internal abnormalities such as thyroid dysfunction, collagen diseases, iron deficiency, or malnutrition must be ruled out for diagnosis of FAGA because these disorders may possibly be associated with diffuse hair loss especially in females.

### 9.1.2.3 General Therapeutic Outline

The therapies available for AGA and FAGA include topical reagents, oral drugs, and hair transplantation. Wigs are mentally helpful for the patients, because they often suffered from mental stress or depression due to hair loss. Overall, the algorithmic regimen was proposed as an expert opinion [59] (Fig. 9.1.4).

### 9.1.2.4 Current Established Therapies

FDA approved only two medications, oral finasteride and topical minoxidil, to be effective for AGA or FAGA.

#### 9.1.2.4.1 Finasteride

Finasteride (1 mg/day), type II 5α-reductase inhibitor, administrated *per os* is widely available for AGA in the world. In Japan, the dose of 0.2 mg/day is also used. This reagent inhibits the conversion from testosterone to potent dihydrotestosterone, which causes AGA pathogenesis [60]. The open trial for 3 years in Japan revealed that around 80% patients obtain the increase of hairs and the efficacy rate (at least maintenance of hairs) was 99% [61]. However, finasteride is contraindicated for young females, because teratogenicity might be caused if they are pregnant. Finasteride is not effective for postmenopausal FAGA at a regular dose.

#### 9.1.2.4.2 Minoxidil

Minoxidil is an adenosine-triphosphate-sensitive potassium channel opener, which caused hypertrichosis by its oral intake and thus 1, 2, and 5% minoxidil lotion is
effective for AGA and FAGA [62]. Minoxidil exerts its effect through production of VEGF mediated by adenosine [63].

### 9.1.2.4.3 Other Agents for FAGA

Spironolactone and cyproterone acetate, which block the androgen receptor, are of benefit for FAGA [64, 65].

### 9.1.2.4.4 Hair Transplantation

In 1939, Dr Shoji Okuda first published the modern hair transplantation technique by punch grafting [66]. Thereafter, the new devices and techniques have been developed and so far the best way to obtain natural appearance is transplantation of follicular units from nonbald occipital skin (Fig. 9.1.5) to bald scalp skin (Fig. 9.1.6).

[Fig. 9.1.4 Algorithm of treatment for AGA [3]]

[Fig. 9.1.5 Follicular units from occipital skin (by courtesy of Dr Sotaro Kurata)]
9.1 Hair Diseases (Alopecia Areata and Androgenetic Alopecia)

9.1.2.5 Experimental Approaches

9.1.2.5.1 Ketoconazole Lotion

Open trial of topical ketoconazole (2%) with shampoo suggested that it is effective in relatively young males with AGA, although the efficacy rate is limited [67].

9.1.2.5.2 Finasteride for FAGA

Although finasteride is contraindicated for young female as mentioned earlier, finasteride (2.5 mg/day) associated with an oral contraceptive was reported to be effective for FAGA in premenopausal women [68].

9.1.2.6 Complications to Avoid

There is no severe complication associated with AGA. FAGA could possibly be complicated with hormonal abnormalities including polycystic ovary syndrome. In addition, the patients especially with FAGA are complicated with mental distress, which should be carefully followed up.

Take Home Message

For AGA, the main two therapies, finasteride and minoxidil, are established and widely available at present. However, so far minoxidil is the only treatment established for FAGA and the diagnosis for this condition is still difficult in some cases. Studies to elucidate the pathophysiology of FAGA and to develop new therapeutic strategies will be further needed.

9.1.2.7 Global Variations

In AGA of Asian males, vertex hair loss is often predominantly seen, compared with Caucasian.

References

51. Hibberts NA, Howell AE, Randall VA (1998) Balding hair follicle dermal papilla cells contain higher levels of androgen receptors than those from non-balding scalp. J Endocrinol 156:59–65
53. Randall VA, Thornton MJ, Messenger AG (1992) Cultured dermal papilla cells from androgen-dependent human hair follicles (e.g. beard) contain more androgen receptors than those from non-balding areas of scalp. J Endocrinol 133: 141–147
9.2.1 Nail Psoriasis

Key Features

- Psoriasis limited to the nails may be difficult to diagnose.
- Psoriasis is limited to the nails making it harder to diagnose.
- Biopsies are not always helpful in confirming the diagnosis.
- Nail bed psoriasis is easier to treat than nail matrix psoriasis.
- The list of therapeutic options now includes the biologic agents.

9.2.1.1 Etiology and Pathophysiology

Nail psoriasis has the same pathophysiology as skin psoriasis, which is now considered to be a T-cell mediated disease. Specifically, psoriasis is categorized as a T-helper 1 (Th-1) disease, in which activated T-cells release Th-1 cytokines (IL-2, IFN-γ, and TNF-α) promoting cell-mediated immunity. T-cells are activated from a naïve state when presented with a trigger antigen concurrently with costimulation. Both antigen presentation and costimulation are carried out by Langerhans cells and dermal dendritic cells, which are the antigen presenting cells (APC) of the skin. The exact nature of the trigger antigen(s) is still unknown. Costimulatory signals are transmitted through the binding of a number of surface ligands on APC to specific receptors on the naïve T-cells (Fig. 9.2.1).

Some of the biologic agents discussed in section (9.2.1.5) act by blocking costimulatory signals. Following activation, T-cells undergo clonal expansion. From then on, any encounter between activated T-cells and the trigger antigen induces Th-1 cytokines release, ultimately leading to the epidermal proliferation and inflammation seen in psoriatic lesions. Psoriasis patients may be genetically predisposed to mount such an immunologic reaction [1].

9.2.1.2 Clinical Characteristics and Diagnosis

Nail changes in psoriasis may reflect nail bed involvement (“oil drop” sign or salmon patches, which are pathognomonic, onycholysis, subungual hyperkeratosis, and splinter hemorrhages) or nail matrix involvement (red dots in the lunula, deep nail plate pits, leukonychia, and total crumbling of the nail plate) by the disease and may be quantified using the NAPSI score [2, 3] (Figs. 9.2.2 and 9.2.3).

Classical signs are less evident in toenail psoriasis, which is often hard to distinguish clinically from toenail onychomycosis. To add to the confusion, the two conditions that often coexist as psoriatic nails may be infected with dermatophytes. Fortunately, the vast majority of patients with nail psoriasis also have skin psoriasis, which will give hint to the diagnosis. In the small percentage of patients in whom the disease is limited to the nails and the diagnosis is doubtful, a nail biopsy could
be of value. However, psoriasis and onychomycosis share many histopathologic features, and it is often hard to classify a PAS specimen as onychomycosis or as psoriasis with superimposed fungal infection [2, 4].

### 9.2.1.3 General Therapeutic Outline

Therapeutic options for treating nail psoriasis include topical, intralesional, and systemic therapies. Topical therapy is a good option for patients with mild disease and with multiple nail involvement. Intraleisional injection is an ideal option for patients with only a single or a few nails involved, and in patients reluctant to comply with daily topical application regimens. Systemic therapy is usually reserved for patients with severe nonresponding nail psoriasis or patients with concurrent diffuse cutaneous involvement.

### 9.2.1.4 Current Established Therapies

#### 9.2.1.4.1 Topical Therapy

Fingernail psoriasis generally responds better to topical therapy than toenail psoriasis. Also, psoriatic
changes, secondary to nail matrix involvement are less likely to improve, probably owing to suboptimal drug delivery to the nail matrix by topical formulations. Hence, patients with predominantly nail bed psoriasis benefit the most from topical therapy as do those with involvement of the nail folds. Steroids and steroid/salicylic acid ointments give good results. The nail plate may need to be clipped back for proper application of the ointment to the nail bed. Steroid solutions, although cosmetically more pleasing and easier to apply, are invariably less effective [5]. A concentrated steroid lacquer formulation (8% clobetasol propionate) has been shown to benefit even nail matrix psoriasis [6]. Calcipotriol (vitamin D₃ derivative) ointment is comparable with topical steroids in efficacy when treating regular nail psoriasis and more effective than steroids when treating pustular psoriasis [7, 8]. Furthermore, the use of topical calcipotriol as an adjunct to systemic therapy in the treatment of severe nail psoriasis and pustular nail psoriasis has been shown to limit the frequency and severity of relapses [8]. Tazarotene 0.1% gel and formulations of cyclosporine A (70% oily preparation) and 5 fluorouracil (1% 5-FU in propylene glycol or in 20% urea) have also been used with some success in the treatment of nail psoriasis [5, 9].

### 9.2.1.4.2 Intralesional Therapy

Intralesional steroid injection is effective in treating nail psoriasis. Through injection, steroids can be delivered directly to the nail matrix yielding a better therapeutic outcome for patients with predominant nail matrix psoriasis than topical therapy. Triamcinolone acetonide is usually used at 2.5–3.0 mg/mL and it is diluted using 1% plain lidocaine to minimize patient discomfort. Using a cold spray to numb the area directly before injecting also helps. The nail matrix and nail bed are injected through the proximal and lateral nail folds, respectively. The number of injections per nail (1–4), volume per injection (0.1–0.3 mL), and frequency of injections (every 1–3 months) depend on the concentration used and the severity of the disease [2, 5]. One approach is to inject the nails monthly at the initiation of therapy, and then less frequently as clinical response becomes noticeable.

### 9.2.1.4.3 Systemic Therapy

Methotrexate and cyclosporine are usually reserved for patients with concomitant cutaneous psoriasis. Acitretin is especially useful in the treatment of pustular nail psoriasis and the usual dose of administration is 0.2–0.3 mg/kg/day. PUVA therapy is less effective [2, 5].

### 9.2.1.5 Biologic Approaches

Biologic response modifiers work at various stages of the immunological cascade behind psoriasis (Fig. 9.2.1). Efalizumab and alefacept prevent naïve T-cell activation by blocking costimulatory signals transmitted through LFA-1 and LFA-3, respectively. Infliximab, adalimumab, and etanercept block the major Th1 cytokine TNF-α (or its receptor) [10]. The effectiveness of these agents in the treatment of nail psoriasis has only been investigated in few small series. Specifically, infliximab induced a complete remission in all patients after 5 doses in a series of 25 patients. The remission was maintained 12 weeks after the last dose [11]. In a smaller series of 15 patients with lower NAPSI scores, alefacept improved the average score by 39% after 12 doses (no long-term follow-up) [12]. The role of biologics in the current management of nail psoriasis is yet to be defined.

### 9.2.1.6 Complications to Avoid

The prolonged use of steroids, whether topically or intraleesionally, carries the risk of skin and distal phalynx atrophy. Intraleational steroid injections may additionally be complicated by subungal bleeding with associated pigmentedry changes, which take some time to resolve [2, 5]. The use of higher dosages of acitretin (>0.3 mg/kg/day) increases the risk of paronychia and pyogenic granuloma formation. Acitretin therapy may also cause pathological thinning and brittleness in nails that are not hyperkeratotic at the onset of treatment [2, 5, 8]. There are reports of the anti-TNF-α biologic agents occasionally inducing psoriasiform lesions. Nail changes including oil spots, subungal hyperkeratosis, onycholysis, and nail pits have all been described in the setting of such paradoxical responses [13].
9.2.2 Onychomycosis

Key Features

- Trichophyton rubrum is the most common cause of onychomycosis.
- The most widely used diagnostic tests are KOH examination, PAS, and culture.
- Systemic therapy is needed when onychomycosis involves the nail matrix.
- Combination therapy has multiple advantages over oral or topical monotherapy.
- Terbinafine is the most effective oral antifungal agent for dermatophytes.
- Systemic azoles inhibit cytochrome P450 and may interfere with other drugs.
- In some cases, prolonged treatment duration or booster doses are needed.

9.2.2.1 Etiology and Pathophysiology

Onychomycosis is a fungal infection of the nail unit that may be caused by dermatophytes, yeasts, and non-dermatophytic molds (NDM). Dermatophytes are by far the most common cause of onychomycosis with Trichophyton rubrum being the most commonly isolated pathogen [15]. Dermatophyte infective forms include hyphae, spores, and matted conglomerations of hyphae (referred to as dermatophytomas). An exophytic fungal ball, made up of a cushion of hyphal elements covered by spores (referred to as sporodochium), has also been recovered from an onychomycotic nail [16]. NDM and yeasts are less common causes of onychomycosis. NDM are saprophytes that are likely to invade the already damaged nails, which may also be true for yeasts as well. Yeasts are a major cause of fingernail onychomycosis. The most commonly isolated NDM and yeast are Scopulariopsis brevicaulis and Candida albicans, respectively [15].

9.2.2.2 Clinical Characteristics and Diagnosis

Five main clinical subtypes of onychomycosis have been described. The subtype observed in a particular patient is a function of the nature of the causative organism and the site of nail unit invasion by the pathogen. Distal and lateral subungual onychomycosis (DLSO) is the most common subtype. Toenail infection is up to 20 times more common than fingernail infection. The preliminary results of the European Onychomycosis Observatory (EUROO) study have shown that the great majority of patients present with 1–4 nails affected and 75% of them do not have nail matrix involvement [15, 17].

Accurate diagnosis of onychomycosis can be problematic. Although advanced diagnostic modalities are available, mycological examinations (KOH examination and culture) remain the most commonly used diagnostic methods by virtue of their uncomplicated nature and relatively low cost. However, false-negative rates are high and depend largely on sample collection and preparation methods [18]. Counterstaining with Chlorazol black E and Acridine Orange, which are all fungal specific, may increase the sensitivity and specificity of KOH examination. Acridine Orange is a fluorescent dye and requires the use of fluorescence microscopy [19]. Histomycology (histologic analysis of periodic acid Schiff (PAS)-stained nail clippings) significantly adds to the sensitivity of KOH examination and nail cultures [18]. A silver stain may allow
better visualization of fungal morphology when the
PAS stain is ambiguous [20]. Fungal culture is the only
test that can identify the offending pathogens, while
histomycology is helpful in differentiating the patho-
genic fungi from the nonpathogenic fungi by showing
the extent of nail invasion [18].

9.2.2.3 General Therapeutic Outline

A frequent source of discomfort and embarrassment is
that onychomycosis may also predispose patients to
serious medical disorders [21]. Therapeutic options
include topical and systemic antifungals. Systemic
antifungals offer the best chance for a cure. However,
the results obtained can be further enhanced by adding
a topical antifungal (combination therapy). Topical
antifungals may be used as monotherapy for the treat-
ment of mild disease and for long-term prophylaxis. In
some cases, nail plate debridement or surgical avulsion
may help to improve symptoms and to decrease fungal
load [22, 23].

9.2.2.4 Current Established Therapies

9.2.2.4.1 Topical Therapy

Topical monotherapy may be initiated in patients
without matrix involvement who present with four
diseased nails or fewer, provided that onychomycosis
is limited to the distal half of the nail plate(s) [23]. A
good percentage of patients satisfy these criteria at
presentation (see Sect. 9.2.2.1). The most effective
topical antifungals are lacquer formulations, which
allow better permeation of the nail plate and achieve
higher concentrations in the nail bed. Ciclopirox
olamine and amorolfin are two such preparations,
which exhibit both fungicidal and fungistatic activi-
ties against a broad spectrum of fungi. Ciclopirox
olamine acts as a chelating agent and affects the mito-
ochondrial electron transport process, while amorolfin
blocks fungal ergosterol synthesis. Compared to older
topical formulations, improved cure rates could be
achieved when using lacquers in patients with mild
disease [22–24].

9.2.2.5 Systemic Therapy

Oral antifungals are needed when the matrix or the pro-
Ximal nail plate are involved. Commonly used antifungals
include terbinafine (an allylamine), itraconazole (a triaz-
ole), and fluconazole (a bis-triazole). All three drugs
interrupt ergosterol synthesis and have a broad spectrum
of activity. Terbinafine is the most potent in vitro and the
only one, which is fungicidal against dermatophytes
rather than fungistatic. Itraconazole and fluconazole are
usually administered in pulses (400 mg/day for 1 week/
month and 150–450 mg once/week, respectively) whereas
terbinafine has been shown to be effective when adminis-
tered daily (250 mg/day). Although the recommended
treatment duration is 12 weeks for toenail disease
(8 weeks for fingernails), some patients may require
additional dosages [22, 25, 26].

9.2.2.5.1 Combination Therapy

Combination therapy provides better drug delivery,
synergistic antifungal activity, wider antifungal spec-
trum coverage, shorter treatment duration, and may
prevent the emergence of resistant fungal strains.
Studies have shown that this translates into higher cure
rates and increased cost effectiveness [23, 24]. Although
most studies on combination therapy involve amor-
olfin, ciclopirox olamine shares the same theoretical
advantages, and a recent study has confirmed the syn-
ergism between ciclopirox olamine and itraconazole
in vitro [27]. Combination therapy is more commonly
used by dermatologists than general practitioners [15].

9.2.2.5.2 Other Therapies

Nail plate debridement, mechanical avulsion, and
chemical avulsion (40% urea ointment) are sometimes
used to supplement antifungal therapy. The role of
these interventions is to alleviate pain in markedly
thickened or distorted nails. Another role is to decrease
the fungal load when suspecting dermatophytopomas,
which are predictors of therapeutic failure, since these
conglomerations of hyphae are not penetrated by the
antifungal drugs [22, 23]. Regular nail trimming pre-
vents the formation of undernail sporodochia and
hence achieves a similar end [16].
9.2.2.6 Experimental Approaches

9.2.2.6.1 Boosted Therapy

Since dormant spores are thought to be a major reason behind treatment failures and relapses, Pierard et al. tried to optimize their growth in “boosted regimens”, which consisted of attaching pieces of Sabouraud agar to the nail during the course of antifungal therapy. Preliminary results were promising (mycological cure rate of >90% with oral therapy) [22].

9.2.2.6.2 New Antifungals

The role of the newer azoles voriconazole, ravuconazole, and posaconazole in the treatment of onychomycosis is not yet clear.

9.2.2.7 Complications to Avoid

Persistent disease is a complication encountered in at least 20–25% of patients with onychomycosis. Therapeutic failure may be secondary to misdiagnosis, extensive disease, inadequate treatment, or the underlying medical and behavioral factors [28].

The use of itraconazole and fluconazole in patients on multiple medications should be avoided as these azoles inhibit the cytochrome P-450 enzyme 14α-demethylase, and hence may cause drug interactions. Onychomycosis caused by unusual fungal pathogens (Fusarium species) in immunocompromised patients should be treated aggressively because of the risk of systemic dissemination in this patient population [29].

Uncontrolled growth and dissemination of resistant fungi is a theoretical risk, which has limited the popularity of boosted regimens [22].

9.2.2.8 Global Variations

To the best of our knowledge, no global variations in the management of these nail disorders have been identified.

References


Take Home Message

- Management of onychomycosis should always begin with an accurate diagnosis and with the identification of the pathogen. The therapeutic guidelines are helpful most of the time, but therapy often has to be tailored to the individual patient.
9.3.1 Etiology and Pathophysiology

9.3.1.1 Introduction

Hyperhidrosis is perspiration in excess of the physiological amount necessary to maintain thermal homeostasis [1]. Primary or idiopathic hyperhidrosis is characterized by excessive sweating affecting the soles, palms, and axilla in various combinations and with varying degrees of severity [2]. Secondary hyperhidrosis can be focal or generalized. There are numerous disease states leading to this condition. These are listed in Table 1 and should be excluded before diagnosing a patient with primary hyperhidrosis. Table 1 also lists pertinent lab tests to help exclude these diagnoses if they are suspected (Table 9.3.1).

9.3.1.2 Background

There are 2–3 million eccrine sweat glands; these are the glands that are responsible for hyperhidrosis [3, 4]. Eccrine glands are in higher density on the soles of the feet and the forehead, followed by the palms and the cheeks [5]. The eccrine glands are coiled and open directly onto the surface of the skin through sweat pores. Eccrine glands secrete an odorless clear fluid that serves to aid the regulation of body temperature by allowing heat loss by evaporation [5]. A person can produce up to several liters of sweat per hour and 10 L/day [5, 6].

Apocrine sweat glands are confined to a few areas, mainly the axilla and urogenital region. They usually open onto hair follicles, and produce small amounts of sweat that is not thought to contribute to hyperhidrosis. They produce a thick, odorless fluid that undergoes bacterial decomposition, leading to substances with strong odors. For nonhuman species, apocrine sweat provides pheromone signaling that is important in mating, parenting, and other interactions; it is unclear what the role is for apocrine sweat in humans [7].

Both eccrine and apocrine sweat glands are innervated by postganglionic sympathetic fibers. The major neurotransmitter for eccrine glands is acetylcholine; catecholamines regulate apocrine glands. Spinal cord segments T2–T8 provide innervation to the skin of the upper limbs, T2–T4 innervate the skin of the face, T4–T12 innervate the skin of the trunk, and T10–L2 innervate the skin of the lower limbs [5].

9.3.1.3 Histopathology

Sweat glands in patients with hyperhidrosis are not histopathologically different from those in normal
patients. There is not an increase in the number or size of glands; they are morphologically and functionally normal eccrine glands. Hyperhidrosis is caused by an increased function of the sweat glands rather than hypertrophy [8].

### 9.3.1.4 Pathophysiology

The thermoregulatory center in the hypothalamus controls body temperature by regulating eccrine sweat output and blood flow to the skin. This center responds not only to changes in core body temperature, but also to hormones, endogenous pyrogens, physical activity, and emotions [7, 9]. The sweat glands on the palms and soles appear to be activated primarily by emotional stimuli, receiving input exclusively from the cortex, while axillary sweating is stimulated by both thermoregulatory changes as well as emotional stimuli [3, 10–12]. Therefore, palmoplantar hyperhidrosis, unlike generalized hyperhidrosis, does not occur during sleep or sedation.

### 9.3.1.5 Etiology

Emotional sweating is thought to be an outdated function that was important when hunting animals or fighting enemies. Physiologic amounts of sweat on the palms and soles can improve friction by controlling the humidity of the stratum corneum, leading to an improved grip [6]. Generalized sweating cools the body when intense physical activity is expected. In addition, increased eccrine sweat output in the axilla produced by emotional stimuli will allow natural odors from prior apocrine gland secretion to aerosolize and function as pheromone signals. Patients with primary hyperhidrosis have a higher-than-normal basal level of sweat production as well as an increased response to normal stimuli such as emotional or physical stress.

<table>
<thead>
<tr>
<th>Causes</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile illness, Infection</td>
<td>CBC, HIV test, Blood Culture</td>
</tr>
<tr>
<td>Endocrine or metabolic disorders (thyrotoxicosis, diabetes mellitus,</td>
<td>Thyroid function tests, blood glucose levels,</td>
</tr>
<tr>
<td>hypoglycemia, gigantism, acromegaly, pheochromocytoma, gout)</td>
<td>urinary catecholamines, uric acid levels</td>
</tr>
<tr>
<td>Physiologic (over-clothing, exercise, environment, menopause)</td>
<td></td>
</tr>
<tr>
<td>Drugs and toxins (propranolol, physostigmine, pilocarpine, tricyclic</td>
<td>–</td>
</tr>
<tr>
<td>antidepressants, venlafaxine, antiemetics, narcotic withdrawal)</td>
<td>Drug levels</td>
</tr>
<tr>
<td>Neoplasm (carcinoid tumor, intrathoracic neoplasm, Hodgkin’s disease,</td>
<td>Chest radiography, CBC</td>
</tr>
<tr>
<td>Pheochromocytoma, CNS lesion)</td>
<td></td>
</tr>
<tr>
<td>Gustatory or olfactory hyperhidrosis (associated with Frey syndrome,</td>
<td></td>
</tr>
<tr>
<td>encephalitis, syringomyelia, diabetic neuropathies, herpes zoster</td>
<td></td>
</tr>
<tr>
<td>parotitis, and parotid abscess)</td>
<td></td>
</tr>
<tr>
<td>Spinal cord injuries</td>
<td></td>
</tr>
<tr>
<td>Compensatory hyperhidrosis</td>
<td></td>
</tr>
<tr>
<td>Respiratory or cardiovascular disorders disease or failure (TB)</td>
<td>A purified protein derivative (PPD) test</td>
</tr>
<tr>
<td>Chronic alcoholism</td>
<td></td>
</tr>
<tr>
<td>Eccrine nevus and eccrine angiomatous hamartoma (abnormal number</td>
<td>Skin biopsy</td>
</tr>
<tr>
<td>and/or distribution of otherwise normal eccrine glands)</td>
<td></td>
</tr>
<tr>
<td>Harlequin syndrome (unilateral hyperhidrosis and flushing,</td>
<td></td>
</tr>
<tr>
<td>predominantly induced by heat or exercise) sympathetic deficits</td>
<td></td>
</tr>
<tr>
<td>usually limited to the face</td>
<td></td>
</tr>
<tr>
<td>Rare causes (nail-patella syndrome, familial dysautonomia, Riley-Day</td>
<td></td>
</tr>
<tr>
<td>syndrome, POEMS, burning feet syndrome, pachydermoperiostosis,</td>
<td></td>
</tr>
<tr>
<td>pachynichia congenital, apert syndrome, papillon lefevre)</td>
<td></td>
</tr>
</tbody>
</table>
9.3 Hyperhidrosis

One of the underlying mechanisms for a lower threshold and exaggerated response in patients with hyperhidrosis may be excessive sympathetic activity.

9.3.2 Clinical Characteristics and Diagnosis

9.3.2.1 Primary Hyperhidrosis

Primary hyperhidrosis is defined by the excess sweating present for at least 6 months duration without apparent cause with at least two of the six features listed below [13].

1. Excessive, bilateral, relatively symmetric sweating in the axilla, palms, soles, or craniofacial region.
2. Impairment of daily activities.
3. Frequency of at least one episode per week.
4. Age of onset under 25 years of age
5. Positive family history
6. Cessation of focal sweating during sleep

Visible signs of hyperhidrosis are often clearly evident. If direct visualization of the affected areas is desired, the iodine starch test may be used. After the skin is cleansed and dried, iodine is applied and then dusted with a fine starch powder. Perspiration combines with the iodine and glucose in the starch to produce a black color.

9.3.2.2 Secondary Hyperhidrosis

In secondary hyperhidrosis the symptoms are due to one of a large number of medical conditions listed in Table 1. Hyperhidrosis beginning later in life should prompt a search for secondary causes such as systemic diseases, adverse effects of medication use, or metabolic disorders. This form of hyperhidrosis is usually generalized or focal and asymmetric.

9.3.3 General Therapeutic Outline

There are several treatment options available for primary hyperhidrosis. These include topical agents, oral medications, iontophoresis, botulinum toxin injections, and surgery. Treating secondary hyperhidrosis is facilitated when the underlying condition is identified.

9.3.4 Current Established Therapies

9.3.4.1 Topical Therapy

There are various treatments such as aluminum chloride, boric acid, topical anticholinergics, resorcinol, 2–5% tannic acid, potassium permanganate, formaldehyde, methenamine, and glutaraldehyde. Prescription strength aluminum chloride hexahydrate antiperspirants such as Drysol (20% aluminum chloride hexahydrate in absolute anhydrous ethyl alcohol) or Xerac (6.25% aluminum tetrachloride) appear to be the most effective topical therapy to treat mild to moderate axillary, palmar, or plantar hyperhidrosis [9, 13].

The mechanism of action of aluminum chloride is believed to be the production of a complex between keratin in the sweat ducts and the metal ions in the product. This complex obstructs sweat pores and induces atrophy of the secretory cells within eccrine sweat glands [14]. The only contraindication is hypersensitivity; it should not be applied to irritated, broken, or recently shaved skin. This agent is applied to dry skin nightly until clinical relief is achieved. Effects should be noted within 1 month, at which point the intervals between applications should be lengthened. To minimize irritation, the remainder of the medication should be washed off when the patient awakes. In addition, low potency steroid creams such as 1–2.5% hydrocortisone can help alleviate any irritation that occurs.

There are several studies showing the efficacy of aluminum chloride hexahydrate in axillary, palmar, and plantar hyperhidrosis [11, 15–17]. Daily applications on a continuous basis may be necessary for efficacy, which can be time-consuming and lead to decreased compliance. Topical medications may fail to adequately control hyperhidrosis, especially in more severe cases.

9.3.4.2 Systemic Therapy

Systemic agents used to treat hyperhidrosis include anticholinergic medications such as propantheline bromide (Probanthine®), glycopyrrolate (Robinul®),
oxybutynin (Ditropan®), and benztropine (Cogentin®). These are effective because they inhibit the binding of acetylcholine (the neurotransmitter responsible for the secretion of sweat from eccrine glands) to the cholinergic receptor. Clinical effects usually occur within days, however, adverse effects such as mydriasis, blurry vision, dry mouth and eyes, urinary retention, and constipation limit the use of these medications.

In patients with hyperhidrosis related to specific emotional events, beta-blockers or benzodiazepines may be helpful in reducing the emotional stimulus that leads to excessive sweating. Benzodiazepines and other anxiolytics may reduce anxiety, thereby blocking the emotional trigger stimulus that can result in hyperhidrosis. These should be used on a limited basis for short periods of time prior to a specific stressful situation due to potential for dependency and side effects such as lethargy and drowsiness. Unfortunately, most patients with moderate to severe hyperhidrosis find both topical and systemic agents ineffective, leading them to seek other options [9, 10, 18].

### 9.3.4.3 Iontophoresis

Iontophoresis is the introduction of an ionized substance through intact skin by direct current and was first reported in 1952 [19]. The patient uses a battery-powered device to deliver a low direct current of electricity to the hands or feet while the patient’s body is immersed in water. This treatment is useful for palmar and plantar hyperhidrosis, but is difficult to administer to the axillary areas.

The mechanism of action remains under debate. One hypothesis is that it induces hyperkeratosis of the sweat pores and causes temporary obstruction of sweat flow and secretion [20–23]. Another proposed mechanism is impairment of the electrochemical gradient of sweat secretion [20, 21].

Tap water iontophoresis (TWI) is labor intensive but can be done in a clinic or at home. In palmoplantar hyperhidrosis, the daily treatment of each palm or sole for 30 min at 15–20 mA with TWI has shown to be effective [24, 25]. Six to twelve treatments usually produce the desired effect, after which maintenance therapy can be administered at 1 week to 1 month intervals. Anticholinergic agents can be added to the iontophoresis solution that lengthens the duration of action; however, anticholinergic side effects may occur including dry mouth and mydriasis [26]. Other side effects may include irritation, erythema, vesicle formation, slight pain, temporary paresthesia, as well as minor burns at sites of previously injured skin. These side effects can be related to increased length of time or amperage of the iontophoresis treatment [22–24].

Contraindications include pregnancy, the presence of a pacemaker, or metallic orthopedic implants [13]. Upon initiation of iontophoresis, many patients may experience an aggravation of their symptoms, which subsides after three to five treatments. After successful treatment, symptoms recur after about 1 or 2 weeks without maintenance therapy. With the availability of a device for use at home (the Drionic®), this treatment option is relatively affordable and accessible [24]. There are a few small controlled studies that show the efficacy of this treatment [21].

### 9.3.4.4 Botulinum Toxin

Botulinum toxin type A (BTX-A) is approved by the U.S. Food and Drug Administration for the treatment of axillary hyperhidrosis. BTX-A intradermal injections inhibit the release of acetylcholine from presynaptic nerve endings, blocking the sympathetic cholinergic autonomic fibers that innervate sweat glands. After the starch iodine test is performed to map out the area needing treatment, injections are placed 1.5 m apart over the affected area.

Efficacy can be observed within a week and the duration of anhidrosis induced by botulinum toxin injections varies within a range of 4–13 months [27]. For successful long-term therapy, injections must be repeated. Potential side effects include a transient, slight muscular weakness in muscles of the hand, small hematoma formation at the injection sites, and compensatory sweating (induction of sweating in previously unaffected areas of the body) [28, 29]. The main drawback is that botulinum toxin injections are painful and require the use of an anesthetic when treating palmar hyperhidrosis. Ulnar and median nerve blocks are more effective in preventing pain than topical application of a local anesthetic agent. Application of ice immediately before injection and intravenous regional anesthesia (Bier’s block) can also be helpful [19, 30]. Contraindications include documented hypersensitivity, aminoglycosides, or drugs that interfere with neuromuscular transmission...
since they may potentiate effects. Botox is classified as an agent for which safety during pregnancy has not been established. Many placebo-controlled trials have assessed the safety and efficacy of BTX-A on axillary hyperhidrosis [28, 29, 31–33].

BTX-B also blocks release of acetylcholine; however, while BTX-A cleaves the synaptosome-associated protein 25 kDa, BTX-B inactivates the vesicle-associated membrane protein. BTX-B may have a faster onset of action when compared to BTX-A, however, it appears to be more painful upon administration, may be associated with systemic autonomic side effects (dryness of eyes and mouth), and may have a shorter duration of action [34].

9.3.4.5 Surgical Treatment

Both surgical removal of the eccrine glands (either through excision or subcutaneous liposuction) and surgical sympathectomy have been used effectively to treat hyperhidrosis.

9.3.4.5.1 Sympathectomy

Sympathectomy has been used as a permanent effective treatment for hyperhidrosis since 1920 [35]. Usually, it is reserved as a final treatment option after other options have been tried. Sympathectomy involves the surgical destruction of the ganglia responsible for hyperhidrosis (the second (T2) and third (T3) thoracic ganglia for palmar hyperhidrosis, the fourth (T4) thoracic ganglia for axillary hyperhidrosis, and the first (T1) thoracic ganglia for facial hyperhidrosis). An endoscopic approach to this procedure is favored because of its reduction in complications, surgical scars, and surgical times. The complications associated with this procedure include compensatory sweating, gustatory sweating, pneumothorax, intercostal neuralgia, Horner syndrome, recurrence of hyperhidrosis, and the sequelae of general anesthetic use [11]. Compensatory sweating is much more problematic with T2 sympathetic ganglionic interruption for palmar hyperhidrosis than compared to T4 ganglion interruption for axillary hyperhidrosis. Therefore, performing both of these procedures at the same time is an effective approach that can simultaneously minimize the rate of compensatory hyperhidrosis [36]. Another effective treatment for compensatory sweating is the intradermal injection of botulinum toxin [5, 37]. The risk for permanent sexual dysfunction limits the usefulness of lumbar sympathectomy for plantar hyperhidrosis [9].

9.3.4.5.2 Surgical Removal of Eccrine Glands

Both subcutaneous liposuction and classical surgical excision remove the eccrine sweat glands responsible for axillary hyperhidrosis. Compared with classic surgical excision, subcutaneous liposuction results in less disruption to the overlying skin, producing in smaller surgical scars and a diminished area of hair loss [38]. A recent study on tumescent liposuction with dermal curretage showed this procedure to be effective due to the combination of removing the eccrine sweat glands and the production of dermal fibrosis, which inhibits the function of the remaining sweat glands [39].

9.3.5 Experimental Approaches

A few interventional radiologists in Belgium use CT fluoroscopy to guide injections of phenol in order to safely destroy the nerves responsible for hyperhidrosis. For palmar and axillary hyperhidrosis, saline is first injected to widen the extrapleural space to avoid pneumothorax. Then a flexible needle is inserted into the third intervertebral space that injects phenol into the sympathetic ganglia [40]. Each patient requires two treatments, one for each hand or axilla. The entire procedure is visualized using multi-slice CT fluoroscopy and requires only local anesthesia. In a small number of patients compensatory sweating in the chest or the feet occurred after the procedure. This procedure is reported to be as effective as surgical or endoscopic sympathectomy, but with a much lower complication rate and a reduced cost. The results from this study are still currently under review. This procedure is not currently performed in the United States.

9.3.6 Complications to Avoid

Noninvasive therapies, such as topicals and iontophoresis, are the safest, but results are often short lived or insufficient. BTX-A injections are an excellent
alternative to surgery; however, a hematoma at the injection site or transient thenar muscle weakness may occur. Surgery should be reserved for the most severe cases. Endoscopic sympathectomy has replaced earlier open thoracic procedures as a safer and simpler technique, but complications include Horner syndrome, compensatory hyperhidrosis, scarring, gustatory sweating, pneumothorax, intercostal neuralgia, recurrence of hyperhidrosis, and possible sequelae of general anesthetics [11, 41, 42].

Axillary treatment algorithm
1. Over the counter antiperspirants
2. 10–35% aluminum chloride hexahydrate
3. Injections of BTX-A
4. Surgery

Palmoplantar treatment algorithm
1. 10–35% aluminum chloride hexahydrate or tap water iontophoresis
2. Injections of BTX-A
3. Surgery

9.3.7 Global Variations

Hyperhidrosis is not rare, and while it affects all races, palmoplantar hyperhidrosis has been found to be 20 times more frequent in the Japanese than in any other ethnic group [43, 44]. In the United States, the incidence of hyperhidrosis in adolescents and young adults in a recent survey was reported to be 2.8% [45]. In another study, the incidence among young Israelis was reported to be 0.6–1% [2]. Aside from these few studies, the frequency of hyperhidrosis in the general population is not well documented and requires a more thorough investigation.

References

9.4.1 Melasma

**Key Features**

- Acquired chronic hypermelanosis on the face occurring mainly in women with Fitzpatrick skin types IV–V.

9.4.1.1 Etiology and Pathophysiology

The cause of melasma is unknown, but factors include genetic predisposition, exposure to ultraviolet (UV) light, pregnancy, and hormonal therapy. Estrogen and progesterone are thought to induce melasma as it often develops during pregnancy, among the users of oral contraceptives and among postmenopausal women on hormone replacement therapy (HRT) [1]. Other implicated factors include phototoxic drugs and anticonvulsant medications. A recent study shows that high expression levels of \( \alpha \)-melanocyte stimulating hormone (\( \alpha \)-MSH) [2] and vascular endothelial growth factor (VEGF) [3] in lesional keratinocytes and of stem cell factor (SCF) in fibroblasts [4] result in the activation of lesional melanocytes. This indicates that neighboring cells as well as melanocytes contribute to melasma formation. Furthermore, more accentuated solar elastosis is found in the lesional skin of melasma when compared with adjacent perilesional normal skin, suggesting that accumulated sun exposure is involved in melasma development [5], in addition to exacerbation of the disease.

9.4.1.2 Clinical Characteristics and Diagnosis

Melasma presents as brown to gray macules and patches, with serrated, irregular, and geographic borders. The pigmented patches are usually sharply demarcated and symmetrical (Fig. 9.4.1). Melasma...
has a predilection for areas exposed to sun. The three major patterns of distribution are: centrofacial (cheeks, forehead, upper lip, nose, and chin), malar (cheeks and nose), and mandibular (rami of the mandible) [1]. Wood’s lamp distinguishes epidermal, dermal, and compound (epidermal + dermal) forms of melasma [1]. In epidermal melasma, melanin is deposited in the basal and suprabasal layers, and occasionally throughout the epidermis [5]. In dermal melasma, melanin-laden macrophages accumulate around the superficial and mid-dermal vasculature [1]. The ultrastructure shows increased melanocytes, melanogenesis, transfer of melanosomes, as well as the size and ratio (%) of melanosomes in keratinocytes [1, 5, 6].

### 9.4.1.3 General Therapeutic Outline

Because sun exposure is a key etiologic factor [1], protection from sun exposure is critically important. Broad-spectrum, high-SPF sunscreens must be applied daily [7]. Combinations of topical and oral whitening agents as well as agents that accelerate epidermal turnover elicit superior results when compared with monotherapy [8].

### 9.4.1.4 Current Established Therapies

Hydroquinone (HQ) 2–4% has been widely applied as melasma therapy. It inhibits the conversion of dopa to melanin by inhibiting the activity of tyrosinase [9]. Moreover, it might interfere with DNA and RNA synthesis, degrade melanosomes, and destroy melanocytes [10] under strict sun avoidance, because of the risk of ochronosis-like pigmentation [11]. The combination of HQ 5%, tretinoin 0.1%, and dexamethasone 0.1% (Kligman formula) is the most extensively applied therapy to treat melasma worldwide [8]. The most recent new combination of HQ 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01% has proven more effective than the combination of any two of those agents [12].

### 9.4.1.5 Complications to Avoid

Ochronosis-like pigmentation by HQ and exacerbation of melasma by laser therapy.

### 9.4.1.6 Global Variations

Some European countries prohibit the use of HQ. Topical retinoids such as tretinoin, tazarotene, and adapalene are available in the US and Europe, but not in Japan. Oral tranexamic acid has recently proven effective in a randomized controlled study in Japan [13].

### 9.4.2 Solar Lentigo

#### 9.4.2.1 Etiology and Pathophysiology

Solar lentigo is more prevalent than ephelides (freckles), increases in prevalence and number with age, and is a clinical marker of photodamage. Solar lentigo could be a marker of intermittent high-intensity ultraviolet ray (UVR), cumulative UVR, or mutagenic effects of UVR [14]. Lesional keratinocytes express enhanced levels of endothelin-1 (ET-1) [15] and SCF [16] that stimulate melanocyte proliferation and melanin formation.

#### 9.4.2.2 Clinical Characteristics and Diagnosis

The face and the backs of the hands are affected. In contrast to ephelides, solar lentigo can persist indefinitely.
9.4 Disorders of Pigmentation

without any fading in the absence of sun exposure. The diameter of lentigines ranges from less than 1 mm to a few centimeters, and lentigines can become confluent in areas of severe sun damage. Lentigines are usually light brown, occasionally black (Fig. 9.4.2). Histology shows elongated epidermal rete ridges with club-shaped or budlike extensions, frequent branching and fused rete ridges, as well as a thinned or atrophic epidermis between retes. Melanocytes increase in a linear fashion at the dermo-epidermal junction, but they are not atypical and the nesting patterns are absent [17]. A scant to moderate perivascular mononuclear cell dermal infiltrate is usually associated with scattered melanin-laden macrophages. Electron microscopy shows abundant, abnormally large melanosome complexes in adjacent keratinocytes. When compared with melanocytes in sun-protected skin, melanocytes in solar lentigo have increased melanogenic activity manifested by obvious dopa reactivity, elongated dendrites, large numbers of apparently normal melanosomes, enlarged perikarya with well-developed rough endoplasmic reticula, numerous mitochondria, and hypertrophic Golgi complexes [18].

9.4.2.3 General Therapeutic Outline

Lesional keratinocytes and melanocytes must be destroyed using laser therapy or cryotherapy, and by accelerating the epidermal turnover with topical retinoids and chemicals peeling.

9.4.2.4 Current Established Therapies

Treatment includes laser therapy [especially Q-switched laser: ruby, alexandrite, or frequency-doubled neodymium:yttrium aluminum garnet (Nd:YAG)], topical retinoids, chemical peeling, and cryotherapy [19]. After treatment, sunscreens and blocking agents must be applied to prevent new lesions. Sun must be avoided by wearing protective clothing in addition to blocking agents and sunscreens.

9.4.2.5 Experimental Approaches

Intense pulsed light effectively improves photoaged lesions including solar lentigo [20].

9.4.2.6 Complications to Avoid

The presence of sun-induced pigmented macules in adults is associated with an estimated 2- to 4-fold increase in nonmelanoma skin cancer risk and an estimated 2- to 6-fold increase in melanoma risk [21].

Take Home Message

- The most important way to prevent solar lentigo is to avoid sun exposure.

9.4.2.7 Global Variations

Laser therapy, cryotherapy, and chemical peeling are available worldwide. Topical retinoids such as tretinoin, tazarotene, and adapalene are available in the US and Europe, but not in Japan.
9.4.3 Ephelides (Freckles)

### Key Features

- Small, discrete brown macules usually <0.5 cm in diameter on exposed areas among children and young adults, especially in fair-haired and fair-skinned individuals.

### 9.4.3.1 Etiology and Pathophysiology

Ephelides are noticeable in summer mainly among fair-haired and fair-skinned individuals and may be an autosomal dominant inheritance. Experimental evidence reveals that the minimal freckle dose (MFD) is 6 MED (minimal erythema dose) and may appear after a single sunburn [22]. Freckles help to protect the skin from further UV damage, and may be considered as a sign of photoaging [23]. Ephelides in red-haired individuals are associated with a gene mutation of melanocortin receptor 1 (MC1-R), which results in the dominant synthesis of pheomelanin rather than eumelanin [24].

### 9.4.3.2 Clinical Characteristics and Diagnosis

Ephelides appear in the first 3 years of life and do not occur in areas that are not exposed to the sun or mucous membranes (Fig. 9.4.3). Continued sun exposure increases the degree of freckling. Histologically, the melanocytes are normal or reduced in number when compared with adjacent normal skin, but melanin production is increased owing to UV stimulation. Large numbers of mature melanosomes are evident in dendritic melanocytes. The rete ridge is not elongated and the dermis is normal [25].

### 9.4.3.3 General Therapeutic Outline

Photoprotection is strongly advised. Inactivation of melanocytes by whitening agents and the removal of activated melanocytes by destroying melanocytes with laser therapy or by accelerating epidermal turnover with retinoic acid or chemical peeling are effective.

### 9.4.3.4 Current Established Therapies

Application of HQ 2–4% or combinations of glycolic acid/kojic acid lotion along with retinoic acid will significantly lighten freckles [26, 27]. Q-switched lasers (ruby, alexandrite, or Nd:YAG) can effectively remove freckles, although downtime occurs because of crust formation [28, 29].

### 9.4.3.5 Experimental Approaches

Intense pulsed light is effective with an overall improvement of ephelides without obvious crust formation associated with Q-switched laser therapy [20].

### 9.4.3.6 Complications to Avoid

Ephelides are of clinical significance, because they are associated with both melanoma and nonmelanoma skin
cancer. In red-haired individuals, ephelides, malignant melanoma, and nonmelanoma skin cancer are all closely associated with mutations of the MC1-R gene [24].

**Take Home Message**

- The most important way to prevent ephelides is to avoid sun exposure.

### 9.4.3.7 Global Variations

Laser therapy, cryotherapy, and chemical peeling are available worldwide. Topical retinoids such as tretinoin, tazarotene, and adapalene are available in the US and Europe, but not in Japan.

### 9.4.4 Nevus Spilus (Speckled Lentiginous Nevus)

#### 9.4.4.1 Etiology and Pathophysiology

Nevus spilus may be due to a defect in melanoblasts that populate localized area of the skin because of the possible influence of environmental and genetic factors [21]. Because of the mosaic distribution of extensive nevus spilus, the possibility of mosaicism is also considered [30]. Familial occurrence has been reported [31].

#### 9.4.4.2 Clinical Characteristics and Diagnosis

Present at birth and essentially a uniformly pale brown café-au-lait macule that is well-circumscribed, 2–20 cm, and characterized by serrated or irregular margins containing darker macules or papules 1–2 mm in diameter (Fig. 9.4.4). Wood’s lamp is often necessary to discern the café-au-lait macule background. The distribution assumes such patterns as being sharply demarcated in the midline, and presenting together with Blascko lines, which might reflect embryonic development. This disorder has also been reported as zosteriform lentiginous nevus [32] and nevus on nevus [33]. Microscopy of dopa-incubated split-skin preparations show giant pigment granules in melanocytes or keratinocytes or both. Such giant pigment granules are known as macromelanosome or melanin macroglubules [34]. Light brown and brown macules contain a normal population with an increase in the area and perimeter of whole cells. In contrast, dark brown macules have a significant increase of epidermal melanocytes with a decrease in the area, perimeter, and diameter of cytoplasm as well as the area, length, and breadth of dendrites.

#### 9.4.4.3 General Therapeutic Outline

Longitudinal care for malignant change should be taken although the occurrence is low. Destruction of melanocytes using Q-switched lasers (ruby, alexandrite, Nd:YAG) can improve the appearance [35].

#### 9.4.4.4 Current Established Therapies

Q-switched lasers (ruby, alexandrite, Nd:YAG) might sometimes improve appearance, although hypo- and

---

**Fig. 9.4.4** Nevus spilus

**Take Home Message**

- The most important way to prevent ephelides is to avoid sun exposure.

---

**Key Features**

- Pigmented macules or pigmented papules overlying café-au-lait macules.
- Idiopathic cutaneous anomaly.
hyperpigmentation often develop [35]. Repeated laser irradiation sometimes results in follicular hyperpigmentation with hypopigmentation of the overall area. Therefore, intervals between laser treatments should be carefully considered. Topical retinoid in combination with HQ can lighten the pigment to some extent [36].

9.4.4.5 Experimental Approaches

One small study has shown that intense pulsed light effectively reduces color intensity [37].

9.4.4.6 Complications to Avoid

Nevus spilus can be linked to a melanocytic garden, within which a variety of lesions can grow from junctional nevi to blue nevi to melanoma [38].

Take Home Message

› To improve the appearance is difficult when compared with other hyperpigmented macules. Malignant change should be considered, although it is rare.

9.4.4.7 Global Variations

Topical retinoids such as tretinoin, tazarotene, and adapalene are available in the US and Europe, but not in Japan. Some European countries prohibit the use of HQ.

9.4.5 Postinflammatory Hyperpigmentation

9.4.5.1 Etiology and Pathophysiology

Postinflammatory hyperpigmentation (PIH) represents a pathophysiological response to cutaneous inflammation, such as acne, atopic dermatitis, discoid lupus erythematosus, erythema dyschromicum perstans, fixed drug eruption, generalized drug eruption, idiopathic eruptive macular pigmentation, impetigo, insect bites, irritant and allergic contact and photocontact dermatitis, lichen planus, lichen simplex chronicus, morphea, pityriasis rosea, polymorphous light eruption, psoriasis, burn, abrasive and postsurgical trauma, and viral exanthem [39]. Melanocytes can either be stimulated by the inflammatory process to become hyperfunctional, thus secreting more melanin, or the number of melanocytes can increase. Epidermal hyperpigmentation (such as that associated with acne) occurs when increased melanin is transferred to keratinocytes, whereas dermal pigmentation (e.g., associated with lichen planus and cutaneous lupus erythematosus) occurs when the basement membrane is disrupted causing melanin to fall into the dermis and resides within melanophages [39].

9.4.5.2 Clinical Characteristics and Diagnosis

The lesions are characteristically limited to the site of the preceding inflammation and have indistinct, feathered borders [39].

9.4.5.3 General Therapeutic Outline

Where possible, initial treatment strategies for PIH should manage and control the underlying skin condition. Sunscreen and sun avoidance are important.

9.4.5.4 Current Established Therapies

A clinical trial has found that 0.1% tretinoin cream exerted significant lightening effects in patients with PIH and Type VI skin. However, 50% of the treated patients experienced moderate dermatitis [40]. Another
study of PIH treatment found that adding glycolic acid peels to a topical regimen of HQ 2%, GA 10%, and tretinoin 0.05% cream improved PIH in patients with Type VI skin and that the side effects were minimal [41]. However, peels should be performed with caution on dark-skinned patients owing to a higher risk of hyperpigmentation [42].

### 9.4.5.5 Complications to Avoid

Exacerbation of PIH.

### 9.4.5.6 Global Variations

Topical retinoids such as tretinoin, tazarotene, and adapalene are available in the US and Europe, but not in Japan. Some European countries forbid the use of HQ.

### 9.4.6 Acquired Bilateral Nevus of Ota-Like Macules (ABNOM)

#### Key Features

- Acquired bilateral symmetric blue–brown or slaty-gray macules are commonly seen on the face, mostly in women.

#### 9.4.6.1 Etiology and Pathophysiology

The proposed pathogenesis of the disease is reactivation of extant dermal melanocytes or the manifestation of latent dermal melanocytosis triggered by dermal inflammation, atrophy, or degeneration of the epidermis or dermis. The dermal melanocytes of ABNOM might be attributed to the migration of hair bulb melanocytes into the dermis or to the reactivation of latent dermal melanocytes in the affected areas [43]. Female hormones and exposure to UV might influence the occurrence of ABNOM because of the high ratio of women who develop these lesions [44].

#### 9.4.6.2 Clinical Characteristics and Diagnosis

ABNOM, or Hori’s macules, are characterized by the development of bilateral blue–brown or slaty-gray macules on the face (Fig. 9.4.5). Blue–brown macules can be located on the side of the forehead, temples, eyelids, malar areas, and root, and alae of the nose. Histologically, bipolar or oval dermal melanocytes are scattered in the upper and middle portion of the dermis [43]. Electron microscopy shows that these dermal melanocytes contain many individually dispersed stage II, III, and IV melanosomes. These melanocytes are surrounded by an extracellular sheath [45].

**Take Home Message**

- Control the underlying skin condition and avoid sun exposure and other environmental factors that cause skin inflammation.
9.4.6.3 General Therapeutic Outline

Destruction of dermal melanocytes with Q-switched lasers (ruby, alexandrite, Nd:YAG) might improve the appearance [46].

9.4.6.4 Current Established Therapies

Q-switched lasers (ruby, alexandrite, Nd:YAG) might improve pigmented macules by destroying dermal melanocytes. However, PIH often appears after laser therapy [47].

9.4.6.5 Experimental Approaches

Topical tretinoin and HQ treatment before Q-switched laser therapy have improved outcomes [48].

9.4.6.6 Complications to Avoid

PIH after laser therapy.

9.4.6.7 Global Variations

Topical retinoids such as tretinoin, tazarotene, and adapalene are available in the US and Europe, but not in Japan. Some European countries prohibit the use of HQ.

9.4.7 Nevus of Ota

9.4.7.1 Etiology and Pathophysiology

Nevus of Ota is thought to represent disordered neural crest migration [49]. Melanocytes are thought to be aberrant and become arrested during migration, and remain in the dermis.

9.4.7.2 Clinical Characteristics and Diagnosis

Upper and lower eyelids, and periorbital skin to the temple region, in addition, forehead, zygomatic area, eyebrow, and nose are involved (Fig. 9.4.6). Ocular melanosis is common [50]. Spontaneous regression does not occur. Histology reveals stellate, bipolar dermal melanocytes in the reticular dermis. The long axis of dermal melanocytes is often parallel to the skin surface and is nearly in accordance with the course of the connective tissue. Pigment cells are also present around small blood vessels, sweat glands, and sebaceous glands. Melanophages are rare. Electron microscopy shows stage IV melanosomes in the melanocytes, which are often surrounded by an extracellular sheath [51].

9.4.7.3 General Therapeutic Outline

Q-switched lasers (ruby, alexandrite, Nd:YAG) are effective [52, 53].
9.4 Disorders of Pigmentation

9.4.7.4 Current Established Therapies

Repeated Q-switched laser therapy with sun avoidance results in good clearance of the lesion with minimal risk of scarring.

9.4.7.5 Complications to Avoid

Ocular complications such as melanosis oculi, ocular hypertension [54] and glaucoma of the involved eye, and melanoma [55], although very rare, are mostly seen in Caucasians.

9.4.7.6 Global Variations

There is no global variation in treatment.

9.4.8 Vitiligo

9.4.8.1 Etiology and Pathophysiology

Vitiligo is frequently associated with circulating autoantibodies. Vitiligo can follow emotional crisis, physical injury, and sunburn, and in some cases, it is due to autosomal dominant inheritance. Various hypothetical causes of vitiligo include immune, self-destructive, neural, and composite mechanisms. Furthermore, such mechanisms might be involved in vitiligo as inherent structural defects in melanocytes, the effective role of growth factors [56] in the nonfunctioning of vitiligo melanocytes, the effective role of melatonin [57], and the disorders of T lymphocytes.

9.4.8.2 Clinical Characteristics and Diagnosis

Areas of friction and trauma are characteristically involved, such as the knees, elbows, ankles, backs of...
hands, and feet. Other areas are cheeks, chin, eyes, nose, mouth, anal area, anterior tibial area, flexor of wrists, axilla, and lower back (Fig. 9.4.7). The distribution is symmetrical, but dermatomal arrangement also occurs. Wood’s lamp determine the exact extent of depigmentation. Dopa and haematoxylin−eosin staining shows the absence of melanocytes and occasional lymphocytes at the active margins. Electron microscopy shows keratinocyte vacuolization, with extracellular granular material deposits adjacent to melanocytes in basal keratinocytes. Melanocytes from depigmented and pigmented areas of vitiligo show structural aberrations, with abnormal cytoplasmic filaments, mitochondria, and cell membranes. Melanosome compartmentalization and aberrations of the rough endoplasmic reticulum are often observed [58].

Vitiligo has been associated with various autoimmune diseases, namely Grave’s disease, hyperthyroidism, thyroiditis, myxoedema or thyroid carcinoma, diabetes mellitus, pernicious anaemia, multiglandular insufficiency, halo naevi, and alopecia areata.

### 9.4.8.3 General Therapeutic Outline

Suppression of immunological abnormality with steroids or immunomodulators, activation of reservoir melanocyte migration from hair follicles, melanocyte transplantation in glabrous (nonhair-bearing) skin, or depigmentation of residual normal skin are the treatment choices according to the condition and age of the patient.

### 9.4.8.4 Current Established Therapies

Topical steroid [59] and immunomodulators such as tacrolimus [60] are the simplest of all the available therapies with a reasonable response. Phototherapy including narrow-band UVB (308–313 nm) [61], which penetrates more deeply into the skin and produces less erythema when compared with broad-spectrum UVB, as well as PUVA (psoralen and UVA) [55, 62] is effective for vitiligo lesions with reservoir melanocytes, because phototherapy stimulates melanocyte migration from hair follicles to the epidermis, resulting in repigmentation. Caution should be taken before applying this treatment to ensure that the lesion is on glabrous skin or that the lesional hair is white. Besides narrow-band UVB, an eximer laser (308 nm) [63] can also be used for the spot treatment.

For glabrous skin or for vitiliginous skin with white hairs, a skin transplant can replace the melanocyte reservoir [64]. This technique produces excellent results, but when the condition is severe, especially when combined with a significant immunological abnormality, not only the recipient site, but also the donor site will undergo vitiliginous change (Köbner phenomenon).

Depigmentation with topical monobenzylether of hydroquinone (MBEH) is the therapeutic choice for patients who have extensive vitiligo lesions and where glabrous skin that does not respond to phototherapy is involved [65]. As this strategy results in irreversible depigmentation, it should be carefully selected with the full understanding of the patient that the skin changes will be permanent.

Patches of depigmentation owing to vitiligo on exposed areas can cause cosmetic and social distresses, especially in racially pigmented skin. Cosmetic cover-up also helps diminish such concerns.

### 9.4.8.5 Experimental Approaches

Injection of cultured auto melanocytes into blisters produced by freezing or the application of a vesicant...
produces excellent results, but this technique is expensive and requires specific laboratory facilities for culture methods [66].

9.4.8.6 Complications to Avoid

Possible skin cancer is a consideration, but statistical analysis has shown that the incidence of cancer is not significantly high because of the tendency to cover the depigmented skin [67].

Take Home Message

› Patients with vitiligo should be treated to restore healthy skin and a more normal appearance. Some areas of depigmentation cannot be repigmented by standard medical therapies such as topical steroids or phototherapy. Such limitations should be explained to the patient.

9.4.8.7 Global Variations

There is no global variation in treatment.

References

The main objective of cosmetic dermatologic surgery is to address the visible signs of aging. These include lentigines, vascular lesions, poikiloderma, fat atrophy, and wrinkles. Cosmetic surgery also treats posttraumatic skin changes, such as acne scars and postinflammatory hyperpigmentation.
9.5.2 Clinical Characteristics and Diagnosis

Lentigines, diffuse erythema, and fine telangiectasia can emerge over time, especially in Caucasian patients living in lower latitudes with significant ambient sunlight. Anatomic areas that are the most affected include the central face, lateral neck, upper chest, and arms. On the face, there is commonly a symmetric butterfly-like distribution of erythema and telangiectasia affecting the lower nose and medial cheeks. Reticulated erythema could be seen on the bilateral lateral neck, but the area under the chin and at the nape of the neck is often spared. Lentigines are frequently seen on the lateral cheeks, the temples, and the lateral forehead. Fine speckled and flat lentigines are to be distinguished from macular seborrheic keratoses, which tend to be larger and more asymmetrically distributed; similarly, lentigines are different than melasma, a tan to gray confluent, possibly hormonally mediated pigmentary abnormality of the mid-forehead, upper cheeks, and upper lip. Patients may report that their older relatives have similar but extreme manifestations of the same problems.

Atrophy and facial sagging are associated with normal aging. In recent years, there has been an evolving understanding that volume loss is relatively more instrumental in the manifestation of the aged face than previously believed, and that skin laxity is less so. Early aging, seen in patients in their thirties or forties, is associated with increasing depression of the nasobial folds, emergence of the marionette lines, and hollowing of the infraorbital space. In older patients, perioral and periorbital lines become more deeply etched, with numerous vertical fine lines radiating from the upper and lower vermilion borders, an enlarging crevice separating the chin from the lateral lower cheek, and crow’s feet lines at rest. At the same time, skin sagging becomes evident. Jowls descend, and as the point of the chin remains fixed, a separation known as the pre-jowl sulcus appears between the chin and jowls. High cheekbones flatten out, and the overall shape of the face devolves from an inverted triangle to a rounded, square, or even right-sided (apex at top) triangle. Lips thin out with age. Also the arched lateral brow flattens with age in women. The so-called dynamic creases are lines formed by muscle contraction; these are most often seen on the upper face, including the glabella, forehead, and lateral orbital area (crow’s feet) [21, 23].

Dynamic crease in the glabella and forehead can become evident in women in their twenties, and become deeper over time [1, 9]. Eventually, permanent creases at rest may form at the sites of dynamic creases. Skin texture may also change with aging. Smooth, firm skin may be replaced with very fine wrinkles, thin skin, and a “crepey” morphology.

As facial atrophy proceeds, fat accumulation may occur at other sites on the body. In women, focal fat accumulations are commonly seen at the lateral thighs, upper and lower abdomens, upper arms, and neck. For men, such fat pockets can develop in the flanks (“love handles”), abdomen, and breast. Localized fatty areas can restrict the patient’s ability to find clothes that fit.

Off the face, atrophy can cause blood vessels to be more visible. Dorsal hands can acquire a skeletonized appearance, with visible tendons and vessels. Leg vessels, including superficial red telangiectatic vessels, deeper blue reticular veins, and bulging varicosities, can emerge. As on the face, age-related color and texture changes are noted on the body. Poikiloderma, lentigines, cherry angiomata, seborrheic keratoses, and skin tags may mar the previous smooth, evenly colored skin.

9.5.3 General Therapeutic Outline

Pigmented lesions of the face and body are treated with Q-switched lasers if they are featureless, like lentigines and tattoos, or with destructive modalities, like cryotherapy or light electrodessication and curettage if they have texture.

Superficial vascular lesions are treated with selective lasers and light sources, including pulsed-dye laser, KTP laser, Nd:YAG laser, and intense pulsed light devices. As with the treatment of pigmented lesions with lasers and lights, multiple treatments may be necessary [15, 17, 22, 26].

Facial atrophy is treated with repletion with soft-tissue augmentation materials, or “fillers.” These have variable persistence, with the softest, shortest acting materials used for the most fine, superficial defects [10].

Facial skin sagging, if mild, can be reduced with ablative resurfacing, especially laser resurfacing [13, 14], or nonablative skin tightening with radiofrequency, intense light, or hybrid technologies [7]. Significant skin excess requires excision of this skin by
procedures like rhytidectomy (face lift) or blepharoplasty (eyelid lift). Resuspension of the superficial muscular aponeurosis of the skin (SMAS), the fascial layer under the facial skin, is performed concurrently with face lift.

While focal fat accumulations can be contoured with liposuction, skin resection may be necessary if skin elasticity at the treated site is inadequate for spontaneous contouring. Postoperative compression garments are necessary for the best results [11].

Leg veins require multimodal therapy. Fine telangiectatic vessels are treated with sclerotherapy, and laser is reserved for resistant lesions. Reticular veins may be treated with Nd:YAG laser. Reticular veins and varicosities may also be treated by ambulatory phlebectomy, or “vein stripping.” Reflux at the greater saphenous vein, a potential underlying problem, can be detected by ultrasound and symptomatology, and treated with endovenous laser or radiofrequency ablation 5.

9.5.4 Current Established Therapies

9.5.4.1 Q-Switched Lasers

Lentigines, tattoos, and other flat pigmented lesions can be treated with Q-switched lasers. A number of such lasers are available: frequency-doubled Nd:YAG laser (532 nm), ruby laser (694 nm), alexandrite laser (755 nm), and Nd:YAG laser (1,064 nm). Q-switched devices have pulse durations in the nanosecond domain, and their high power output disrupts the pigmented lesions via a photoacoustic effect [29]. Transiently, the treated areas darken, with a speckled, “cayenne-pepper” like appearance that resolves over a few days, leaving the treated area lighter than before laserig. Tattoos require more intense treatment; pinpoint bleeding can occur, and pain may need to be managed with topical or intraleosional anesthesia. For treatment of lentigines, 3–6 treatments in an interval of 3–4 weeks may be sufficient. Tattoos may never completely resolve, and 10–20 or more treatments may be required for even partial lightening. Some colors, such as yellow, green, orange, or sky blue, may be resistant to laser tattoo removal. Oxidation induced by laser can darken some tattoo pigments.

9.5.4.2 Electrodesication and Curettage, Cryotherapy, or Scissor Excision

Pigmented lesions associated with some texture, like macular seborrheic keratoses, will not respond to laser. Destructive modalities are needed for the treatment of these lesions, as well as more obvious exophytic lesions, such as elevated seborrheic keratosis, dermatosis papulosa nigra, or skin tags. Light electrodesication may be preceded by minimal injection of intraleosional lidocaine with epinephrine for comfort. Cryotherapy should be used sparingly when treating small widely dispersed lesions so as to avoid injury to uninvolved perilesional skin. Scissor excision may be practical and relatively atraumatic for the removal of pedunculated lesions. A gradle scissor and small forceps may further increase precision [27].

9.5.4.3 Pulsed-Dye Laser, KTP Laser, and Intense Pulsed Light Devices

Superficial vascular lesions are effectively treated with lasers and light devices. The pulsed-dye laser (585–595 nm) is a workhorse for the resolution of both facial telangiectasia and erythema. Purpura may be induced when larger caliber telangiectasia are treated with high fluence and brief pulse durations. If bruising must be avoided, multiple consecutive pulses at the same site, the so-called “stacked pulses,” may speed up the resolution of fine telangiectasia. Diffuse erythema, however, can routinely be effectively targeted by pulsed-dye laser at nonbruising settings. KTP laser is useful for addressing telangiectasia of the cheeks, nose, and chin. KTP and pulsed-dye can be used together at the same treatment visit.

Intense pulsed light devices are not lasers but rather bright lamps, which emit at a range of wavelengths, often 500–1,200 nm. Filters help to focus intense light devices to optimize them for vascular lesions. Resolution of redness and vessels with intense pulsed light devices may require more treatments than those with pulsed dye, but light treatments do not bruise and in many states in the US they are readily delegated to nonphysician providers. Long-pulse Nd:YAG lasers are useful for deeper vascular lesions that may be resistant to intense light or pulsed-dye. Nd:YAG lasers have
been used to resolve venous lakes, including those of the lip, and facial reticular veins around the mouth or eyes. Leg veins, especially blue reticular veins, are also amenable to the treatment with Nd:YAG [29]. Resulting intravenous clots may need to be extruded.

9.5.4.4 Prepackaged Injectable Soft-Tissue Augmentation Materials

Facial atrophy is treated with injectable and implantable fillers. During the past decade, a plethora of prepackaged injectable fillers have become available in the US, Europe, Latin America, and Asia. The ease of use, patient tolerability, reversibility, and good efficacy and persistence of these materials have largely marginalized the use of surgically implantable materials, such as 5-PFTE. Similarly, autologous fat transfer has become less popular as prepackaged materials have proliferated. Fat continues to offer many benefits, including its perfect biocompatibility, natural appearance at the recipient site, and availability in large quantities. However, unlike prepackaged materials, fat necessitates a harvesting procedure, in which a mini-liposuction is performed to extract subcutaneous fat from a fat pocket, often on the thighs or abdomen. Given the alternative of a prepackaged injection, patients may decline or at least not prefer this added surgery [10].

Soft-tissue augmentation materials are used to correct a range of facial defects, including acne scars [6, 20], nasolabial folds, marionette lines, vertical lip lines, effacement of the lip vermilion, lip thinning, mental creases, prejowl sulci, cheek wasting, HIV-associated facial lipoatrophy, tear troughs, nasojugal folds, flattened eyebrows, and glabellar creases. Prepackaged injectable materials commonly used in the US and Canada (not all are FDA-approved in the US) are numerous and varied: hyaluronic acid derivatives [30]; calcium hydroxylapatite; [4] human, bovine, and porcine collagens; poly-L-lactic acid; polymethylmethacrylate microspheres; and silicone. Among these, silicone and polymethylmethacrylate provide permanent correction, but short-term and medium-term fillers remain more popular in the US market. Medicolegal concerns and the risk of long-term adverse events have slowed the acceptance of presumably safe soft-tissue augmentation materials in the US. Permanent fillers, as well as thicker or longer lasting temporary fillers (e.g., calcium hydroxylapatite, or poly-L-lactic acid), tend to be injected in the deep dermis or subcutis. Shorter acting fillers such as collagens and hyaluronic acids may be more appropriate for the treatment of superficial defects, placement higher in the dermis, or correction of depressions at delicate areas, such as the lip and infraorbital space. Clinically evident persistence of temporary injectable fillers ranges from 2 to 3 months for human and bovine collagens to 1–2 years for calcium hydroxylapatite and poly-L-lactic acid. Off the face, fillers can be used to camouflage wasting of the dorsal hands or depressed scars.

9.5.4.5 Ablative and Fractional Facial Resurfacing

Full-face resurfacing is still the gold standard for the treatment of severe facial lines, wrinkles, and photodamage. Resurfacing entails removal of the epidermis and partial thickness dermis, and then healing by second intent of these wide, shallow wounds. Carbon dioxide laser resurfacing, dermabrasion, and medium to deep chemical peels with trichloroacetic acid or phenol [12, 28] are comparable modalities for the delivery of this treatment. Laser resurfacing does offer the benefit of more standardized treatment and some tissue shrinkage secondary to thermal coagulation, but may cause longer-lasting posttreatment redness than the other approaches. Dermabrasion is believed by some to be the optimal resurfacing procedure for treatment of acne scarring. In recent years, the prolonged 1–2 week down-time following full-face resurfacing has led to patient dissatisfaction and development of procedures associated with relatively rapid recovery. Er:YAG laser resurfacing or single pass carbon dioxide resurfacing may be followed by only 1 week of mild erythema, crusting, and serous drainage [29]. Plasma resurfacing offers similar downtime and may also provide effective skin tightening around the eyes and mouth [7]. Even faster healing is seen with so-called fractional resurfacing, in which only a portion of the facial skin is ablated during each procedure. A grid pattern is used to target minute zones to be resurfaced, and the energy used can be laser, light, radiofrequency, or ultrasound. Over the course of several treatments, the entire facial skin surface area is treated, but recovery after each individual fractional treatment is swift. Fractional resurfacing has
been effective for the treatment of acne scars and poikilodermatous changes. Resolution of lines and wrinkles, as well as the overall tissue shrinkage, has been less consistently seen with fractional resurfacing.

9.5.4.6 Rytidectomy, Blepharoplasty, and Brow Lifting

When there is significant skin excess, even carbon dioxide resurfacing may be insufficient. Excision of skin and tightening of the underlying fascia Superficial Muscular aponeurotic System (SMAS) may be necessary as an adjunct. Face-lifts for this purpose are now routinely performed by dermatologists employing tumescent anesthesia. Mini-lifts and face-lifts (i.e., rhytidectomies) that dissect above the SMAS have been found to be safe and well-tolerated, with low risk of attendant serious complications, such as facial nerve injury. Upper lip blepharoplasty can be similarly used to reduce skin excess below the brow. Forehead sagging may require a concurrent surgical brow-lift, or chemical and energy brow lift using botulinum toxin and nonablative tightening. Lower lid blepharoplasty can be an appropriate procedure for significant skin or fat pad excess. However, caution must be exercised to avoid over-resection that may result in a skeletonized appearance and perception of the eye as deeply recessed [25].

9.5.4.7 Liposuction

Liposuction using tumescent anesthesia is a highly effective procedure for reducing focal subcutaneous fat accumulations. Areas commonly treated include the jowls, neck, upper arms, male and female breast, upper and lower abdomen, flanks/hips, outer thighs, inner thighs, knees, calves, and ankles. Sterile preparation is required to avoid the risk of infection. First, tumescent anesthesia, a very dilute solution of lidocaine with epinephrine, is infused through small entry sites into the subcutis. Depending on patient body weight, several liters of such fluid can be used. Hemostasis, hydrodissection of fat, and local anesthesia are achieved. Thereafter, so-called aspiration cannulas, long metal tubes with holes at the distal tip, are used to suction subcutaneous fat. Intraoperative oral sedation is employed by some, but is not necessary. Obese patients are not candidates for liposuction, and the procedure does not improve, and can worsen, the appearance of cellulite. Compression garments are worn for several days to weeks after liposuction. Smooth, even skin remodeling is aided by faithful adherence to a garment wearing regimen. At certain sites, such as the arms or abdomen, excess skin may not fully retract after liposuction, and a skin resection procedure may be indicated. It is prudent to wait several months before considering such an additional procedure since skin contraction following liposuction is a gradual process [11].

9.5.4.8 Treatment of Leg Veins

Superficial leg veins can be symptomatic and also unsightly. Reflux due to valvular incompetence of the greater saphenous vein can be diagnosed by Duplex ultrasound combined with patient self-report of discomfort on standing. Treatment is by endovenous ablation using either laser or radiofrequency. After tumescent anesthesia is achieved, a laser or radiofrequency fiber is introduced into the incompetent vessel, and thermal energy is delivered as the fiber is retracted, thus sealing off the vessel.

Telangiectatic leg vessels, or fine red vessels of the legs, can be treated by sclerotherapy. Sclerosant solution is injected with a fine needle directly into the lumen of the offending small superficial vessels. Several treatments are required, and compression therapy may be used after injection. Larger diameter blue vessels, called reticular veins, can also be treated with sclerotherapy. Varicose veins are thicker, unsightly vessels that bulge out from the skin; these may be removed surgically via a procedure called ambulatory phlebectomy, in which small segments are removed via a series of small incisions [5].

9.5.5 Experimental Approaches

Over the last few years, there has been a consistent trend toward minimally invasive procedures that are increasingly safe and associated with diminished
down-time. Current research is focused on areas such as ultrasound skin tightening, noninvasive fat removal, minimally ablative resurfacing, and safe long-term fillers.

Nonablative skin tightening [15, 16, 22, 26] offers the benefits of a face-lift without incisions, scars, or risk of nerve injury. To date, efficacy of these procedures has been low. Ultrasound energy, unlike lights, lasers, and radiofrequency, offers the potential for deep energy delivery to the level of the fascia without corresponding collateral injury to the epidermis and dermis.

Fat removal via liposuction is a safe and effective procedure, but patients are demanding an even faster and safer procedure that does not require incisions. A number of radiofrequency and ultrasound devices are being optimized for this indication. Laser lipolysis, another approach, seeks to melt fat by the insertion of a small laser fiber, either an Nd:YAG or a diode 16.

Minimally ablative resurfacing aims to appropriate the dramatic smoothening and tightening effects of carbon dioxide laser resurfacing without the 1–2 weeks of posttreatment recovery time. Fractional resurfacing procedures split the resurfacing process into several procedures, each of which resurfaces a small fraction of the facial skin. Carbon dioxide fractional resurfacing is now being optimized to improve skin contraction.

New prepackaged injectable soft-tissue augmentation materials have already revolutionized facial augmentation. It remains to be seen if augmentation with permanent fillers can be achieved without delayed-type hypersensitivity response.

### 9.5.6 Complications to Avoid

Common complications associated with cosmetic dermatologic surgery are minor and self-resolving. These include swelling, redness, bruising, and transient pain. Intense laser procedures, and those in patients with ethnic skin, can cause hyper- and hypopigmentation, and scarring. Rare allergic reactions can occur months or years after soft-tissue augmentation. Infections and seromas can rarely occur after liposuction; asymmetry is more common, and can be corrected with a touch-up procedure. Injection of leg veins can cause intravenous clots, and more commonly, telangiectatic mats, which can be treated with laser. Blepharoplasty and lifting procedures can induce scarring. Rarely, blepharoplasty can cause dry eye, and face-lifts can be associated with facial nerve injury.

### Take Home Message

- Cosmetic dermatologic surgery is safe, effective, and convenient for patients. Skin color, texture, laxity, and contour can be improved. While several procedures are used in combination for a desired outcome, the benefits of such an incremental approach include fewer adverse events, rapid recovery, and less tissue injury per treatment.

### 9.5.7 Global Variations

In Europe, lasers are occasionally used for the treatment of melanocytic pigmented lesions (e.g., nevi), but nevi are usually excised in the US. Many soft-tissue augmentation materials available in Europe and Asia are not yet approved for use in the US.

### Further Reading

Part X

Inherited Diseases
Inherited Bullous Diseases

Leena Bruckner-Tuderman and Cristina Has

Key Features

- Inherited bullous diseases represent a heterogeneous group of rare skin disorders, caused by mutations in genes encoding proteins or protein subunits important for the mechanical resistance of keratinocytes and for cell–cell or cell–extracellular matrix adhesion of the epidermis. The hereditary epidermolysis bullosa (EB) is the main disease group in which blistering is the major symptom.

- The common symptoms are skin blistering or peeling, with various degrees of severity and distribution, ranging from localized to generalized forms. Associated features include involvement of skin annexes, mucous membranes, teeth, muscles, or the digestive tract.

- Morphological investigation of skin samples provides evidence for the level of blister formation within the epidermis or the subepidermal basement membrane zone, while immunostaining reveals information on both the precise level of tissue separation and defective proteins, providing clues concerning the molecular basis of the disease.

- Extensive mutation analysis and subsequent identification of gene defects provide accurate diagnostics, and lead to better understanding of the functions of the respective proteins, with the potential for new therapeutic strategies.

- No definitive cure is available for patients with EB at present. Protection against trauma, wound care, surgical correction of complications, adapted nutrition, and psychological support are important. Molecular therapies may represent a potential long-term treatment for these diseases.

10.1 Etiology and Pathophysiology

EB hereditaria, the prototype of inherited bullous diseases, represents a clinically and genetically heterogeneous group of genodermatoses characterized by skin blistering after minor trauma. The diseases are classified into three main categories based on the level of skin splitting and further subtypes on the basis of the clinical severity, which usually reflects the degree of the protein defect (Table 10.1.1) \[4, 11\]. Mutations in 12 distinct genes encoding proteins or protein subunits of the dermal–epidermal junction (DEJ) are responsible for the different subtypes (Fig. 10.1.1 and Table 10.1.1). As inferred by its name, the DEJ joins and maintains the association of two different tissue compartments, the epidermis and the dermis. The DEJ consists of a complex system of adhesive protein suprastructures, which have a typical morphological appearance at the ultrastructural level (Fig. 10.1.1). Recently, the molecular basis of new subtypes has been elucidated: the EB simplex with pyloric atresia, lethal acantholytic EB, and the Kindler syndrome \[15, 16, 30\].

L. Bruckner-Tuderman (✉)
Department of Dermatology, University Medical Center Freiburg, Hauptstrasse 7, 79104 Freiburg, Germany
e-mail: bruckner-tuderman@uniklinik-freiburg.de
Several other genetic multiorgan diseases exhibit skin blistering as an associated symptom (Table 10.1.2). These disorders are heterogenous and must be considered in the differential diagnosis but will not be described in detail in this chapter.

### 10.1.2 Clinical Characteristics and Diagnosis

#### 10.1.2.1 Epidermolysis Bullosa Simplex (Fig. 10.1.2a)

EB simplex (EBS) is the most common EB subtype, accounting for one half of all cases [31]. It is clinically characterized by nonscarring skin blisters caused by minimal trauma. Morphologically, intraepidermal blistering is evident. The clinical spectrum of EBS ranges from mild blistering of the hands and feet in EBS Weber-Cockayne to more generalized blistering in EBS Koebner, EBS Dowling-Meara, and EBS with mottled pigmentation. Dystrophy of some nails may develop, and palmoplantar hyperkeratosis is quite common, but mucous membranes are rarely affected and hair is usually normal. Electron microscopy (EM) and indirect immunofluorescence (IIF) staining of skin sections with antibodies to keratins and proteins of the DEJ have localized the level of splitting to the stratum basale. Mutations in either the gene for keratin 5 (KRT5) or for keratin 14 (KRT14) underlie all the different subtypes. Except for a few families with recessive EBS due to KRT14 mutations, all subtypes have dominant transmission [12].

#### 10.1.2.2 EB Simplex with Muscular Dystrophy

EBS with muscular dystrophy manifests as congenital, generalized blistering associated with late-onset progressive muscular dystrophy. Healing of the skin
Inherited Bullous Diseases

Fig. 10.1.1 The dermal–epidermal junction. Basal keratinocytes, hemidesmosomes, basement membrane, and anchoring fibrils and the corresponding molecular networks are depicted. Focal adhesions attach the actin microfilaments to the plasma membrane through integrin receptors. Desmosomes and their molecular constituents are also represented.

Lesions occur without scarring, but with skin atrophy and nail abnormalities. Mild palmpoplantar keratosis, dental anomalies, and corneal involvement, as well as extensive mucosal erosions and urethral strictures are described in some patients. The onset and extent of the muscle symptoms vary greatly, and in most cases, eventually lead to the patients becoming wheelchair-bound and premature death. EM reveals blistering located low in basal cells just above the hemidesmosomes (HD), HD with hypoplastic attachment plates, and impaired keratin filament insertion into the inner hemidesmosomal plaque. IIF with plectin antibodies shows absence or marked reduction of this protein. This rare autosomal recessive disease is caused by mutations in the PLEC1 gene, which lead to premature termination codons (PTCs) and to absence of plectin,
Table 10.1.2 Inherited diseases with blistering and/or erosions as an associated symptom

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene</th>
<th>Protein</th>
<th>Skin fragility</th>
<th>Other symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin fragility – ectodermal dysplasia syndrome</td>
<td>PKP1</td>
<td>Plakophilin 1</td>
<td>Skin erosions, scalp dermatitis</td>
<td>Congenital ectodermal dysplasia, hypodontia, ankyloblepharon, cleft lip and/or palate</td>
</tr>
<tr>
<td>Skin fragility – woolly hair syndrome</td>
<td>DSP</td>
<td>Desmoplakin</td>
<td>Neonatal skin fragility</td>
<td>Palmoplantar keratosis, wooly hair</td>
</tr>
<tr>
<td>Ichthyosis bullosa Siemens</td>
<td>KRT2e</td>
<td>Keratin 2e</td>
<td>Postnatal blistering</td>
<td>Ichthyosis</td>
</tr>
<tr>
<td>Epidermolytic hyperkeratosis</td>
<td>KRT1, KRT10</td>
<td>Keratin 1 and 10</td>
<td>Blistering and skin erosions postnatal</td>
<td>Ichthyosis</td>
</tr>
<tr>
<td>Laryngo-onycho-cutaneous syndrome</td>
<td>LAMA3</td>
<td>Lamininα3</td>
<td>Slow healing cutaneous erosions</td>
<td>Hoarse cry, granulation tissue in mucosal regions, nail bed and larynx, conjunctival lesions</td>
</tr>
<tr>
<td>Incontinentia pigmenti</td>
<td>NEMO</td>
<td>NF-κB essential modulator</td>
<td>Erythema and skin blistering in the neonate</td>
<td>Dental, ocular and central nervous system involvement</td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
<td>UROD</td>
<td>Uroporphyrinogen decarboxylase</td>
<td>Hyperfragility in sun-exposed areas</td>
<td>Hepatic involvement, hypersideremia</td>
</tr>
<tr>
<td>Hailey-Hailey disease</td>
<td>ATP2C1</td>
<td>Human homologue of an Ca ATP-ase pump</td>
<td>Recurrent blistering predominantly at intertriginous areas</td>
<td>Generalized lesions, warty papules</td>
</tr>
</tbody>
</table>

Fig. 10.1.2 Clinical characteristics of EB subtypes. (a) EB simplex manifests with blisters and erosions on the foot of a 10-year-old girl. (b) Junctional EB non-Herlitz leads to enamel dystrophy in a 12-year-old girl. (c) Scarring and loss of nails in an 18-year-old man with dystrophic EB
both in the skin and in the muscle [23]. An autosomal dominant form of EBS caused by a *PLEC1* missense mutation was found in one large Norwegian family and was coined EBS Ogna [19]. The patients exhibited seasonal acral blistering with onset in infancy and generalized tendency to skin bruising and onychogryphosis, but not muscular dystrophy. Since no other families have been identified so far, the genotype-phenotype correlations of this disease remain elusive.

### 10.1.2.3 EB Simplex with Pyloric Atresia

Thus far, six related patients with the newly identified EBS with pyloric atresia have been described [25, 30]. All of the patients exhibited severe generalized congenital blistering and pyloric atresia, and died from complications of the disease shortly after birth. EM showed cleavage within the lamina lucida [30] or at the base of the basal keratinocytes [25], and HDs were reduced in frequency and were hypoplastic. Immunostaining for plectin was markedly attenuated or absent. Homozygous nonsense, splice site and deletion mutations in *PLEC1* were identified in the affected neonates [25, 30].

### 10.1.2.4 Junctional Epidermolysis Bullosa

#### 10.1.2.4.1 Junctional EB Herlitz

Junctional EB (JEB) Herlitz is one of the most severe EB subtypes, and usually leads to death within the first years of life [24]. The disorder is characterized by widespread erosions and blistering of skin and mucous membranes from birth. The extremities, the scalp, and the face are usually affected early, together with oral and respiratory mucous membranes. The skin is extremely fragile, and normal handling of an affected baby may cause extensive detachment of the epidermis. Typically, laryngeal mucosal blistering leads to hoarseness. Blisters heal without scars, but atrophy develops after recurrent erosions. At some stage, however, the healing of the skin blisters ceases, and large areas of chronic erosions and granulation tissue result. Nails are lost and paronychia-like lesions are characteristic. Tooth enamel is defective, but dental growth is normal. Eventually, fluid and protein loss, combined with poor feeding, cause systemic complications, such as severe anemia, growth retardation, chronic infections and, finally, organ failure. Immunostaining of skin sections is a very useful tool for rapid diagnosis of Herlitz JEB, with characteristic absence or significant reduction in staining with antibodies to laminin 332 (previously laminin 5). EM reveals rudimentary HDs and absence of anchoring filaments. Null mutations in one of the genes encoding the laminin 332 chains underlie this subtype [4]. However, also mutations in the gene encoding collagen XVII, *COL17A1* can cause severe disease manifestations and a shortened lifespan [35].

#### 10.1.2.4.2 Junctional EB Non-Herlitz (Fig. 10.1.2b)

The JEB non-Herlitz subtype comprises all nonlethal JEB forms that are not associated with pyloric atresia. The clinical spectrum ranges from localized to generalized phenotypes with onset at birth or later in life. Typically, JEB non-Herlitz manifests as generalized, life-long blistering of skin and mucous membranes, skin atrophy, alopecia, nail dystrophy, and dental abnormalities [29, 35]. Blister formation occurs at the level of the lamina lucida, and immature HDs are present. Immunostaining for laminin 332 is positive, although frequently attenuated, while collagen XVII staining may be reduced or absent. JEB non-Herlitz is genetically heterogeneous: mutations in one of the laminin 332 genes, *LAMA3, LAMB3,* or *LAMC2*, or in the *COL17A1* gene can result in this phenotype [35].

#### 10.1.2.4.3 Junctional EB with Pyloric Atresia

JEB with pyloric atresia is a rare EB subtype, characterized by skin blistering with pyloric atresia. In severe cases, the condition is perinatally lethal and affected children die of systemic complications, despite surgical correction of the intestinal defect. Mild JEB with pyloric atresia has a favorable prognosis after surgery to correct pyloric atresia. In such cases, skin involvement may be minimal, sometimes with late onset of acral blistering and nail dystrophy. Enamel hypoplasia may be associated with the disease. Mutations in the genes coding for α6 and β4 integrin (*ITGA6* and *ITGB4*) subunits cause JEB with pyloric atresia, with the majority of mutations involving the β4 subunit [2, 35].
10.1.2.5 **Dystrophic Epidermolysis Bullosa (Fig. 10.1.2c)**

10.1.2.5.1 **Dominant Dystrophic EB**

Patients with dominant forms of dystrophic EB (DEB) have a mild clinical phenotype, mostly limited to the skin. Blistering usually occurs at birth or shortly thereafter, and there is a predilection for the extremities. Dystrophy and/or loss of nails are common. IIF of the skin shows normal or reduced collagen VII staining at the roof of a trauma induced blister [4]. EM reveals paucity of anchoring fibrils.

10.1.2.5.2 **Non-Hallopeau-Siemens Recessive Dystrophic EB**

Non-Hallopeau-Siemens recessive DEB is characterized by generalized blistering at birth, mucosal involvement, scarring, dystrophy of teeth, and dystrophy and/or loss of nails. In adulthood, both mild and moderate clinical variants exist. However, mutilations or pseudo syndactylies of hands and feet do not develop. Immunostaining of the skin demonstrates a reduced collagen VII signal at the blister roof [4]. EM reveals rudimentary or absent anchoring fibrils.

10.1.2.5.3 **Hallopeau-Siemens Recessive Dystrophic EB**

Hallopeau-Siemens recessive DEB is one of the most severe EB subtypes. Generalized blistering is present at birth and increases progressively. Poorly healing ulcerations and massive scarring are typical. The synecchia and mutilations of hands and feet, which are characteristic of Hallopeau-Siemens recessive DEB, usually develop early in life. Oral and gastrointestinal involvement leads to malnutrition, which in combination with protein loss through ulcerations, results in growth retardation and anemia. IIF of the skin shows absence or significant reduction of collagen VII, and EM usually reveals complete lack of anchoring fibrils.

All forms of DEB are caused by mutations in COL7A1, the gene coding for type VII collagen. Glycine substitution mutations in the region coding for the triple helical domain of the protein are characteristic of dominant DEB [5] and cause the disease through dominant negative interference. The genetic background of non-Hallopeau-Siemens recessive DEB is heterogeneous, including missense or splice site mutations resulting in in-frame exon skipping in at least one allele. Frequently, non-Hallopeau-Siemens recessive DEB patients are compound heterozygous, and the second mutation often causes a PTC. In contrast, in the majority of Hallopeau-Siemens recessive DEB cases, both mutations cause PTCs which lead to nonsense-mediated mRNA decay and truncated collagen VII polypeptides that are degraded within the cell [17].

10.1.2.5.4 **Lethal Acantolythic Epidermolysis Bullosa**

A single case of a newly recognized syndrome, lethal acantholytic EB, was reported [16]. The newborn showed severe fragility of the skin and mucous membranes, with epidermolysis commencing during delivery, and progressing to 90% of the body surface area within the first days of life, leaving extensive eroded areas. The phenotype also comprised universal alopecia, neonatal teeth, and nail loss. The patient died neonatally due to immense transcutaneous fluid loss. Histology revealed suprabasal clefting and acantholysis throughout the spinous layer, while EM revealed disconnection of keratin filaments from desmosomes. IIF staining for desmoplakin showed an abnormal staining pattern in the patient’s skin. Compound heterozygosity for a nonsense mutation, and a deletion mutation in the desmoplakin gene (DSP) was disclosed as the cause of the disease.

10.1.2.5.5 **Kindler Syndrome**

Kindler syndrome (KS) is a rare autosomal recessive genodermatosis first described in 1954. Since then, around 150 cases have been published, and the causative genetic defect was described in 2003 [15]. The clinical features of KS include congenital skin blistering and mild photosensitivity, both of which improve with age, and an early, generalized, progressive poikilodermat with extensive atrophy. The presence of palmoplantar keratoderma and nail
abnormalities is variable; webbing of the fingers and contractures, gingival fragility and early, rapidly progressive periodontitis occur in some patients. Other mucous membranes, i.e., urethral, anal, esophageal, and genital, may be involved, and the lesions can lead to stenosis. Squamous cell carcinoma has been reported as a complication of KS [36]. EM shows reduplications of the epidermal basement membrane and different levels of blister formation. IIF staining with antibodies against laminin 332 and collagens XVII and VII demonstrate abnormal and discontinuous staining patterns. Mutations in the KIND1 gene, encoding kindlin-1, cause KS [15, 34]; more than 30 loss-of-function mutations have been identified to date [1, 13, 20].

10.1.3 General Therapeutic Outline

To date, the general therapeutic outline for EB disorders consists of wound care based on general principles of wound therapy and of avoidance and minimization of the environmental factors, which induce blistering and complicate wound healing. Care of severely affected patients with extracutaneous involvement requires multidisciplinary management comprising the collaboration of pediatricians, dermatologists, gastroenterologists, dentists, nutritionists, psychologists, ophthalmologists, and other specialists [4]. Patients with recessive DEB and KS have an increased risk for skin cancer, and therefore must be regularly screened [32, 36]. In many countries, EB centers with skilled specialists who have expertise and experience with multiple aspects of EB, offer highly qualitative patient care and diagnostics (for example, see http://geneskin idi.it; or www.netzwerk-eb.de). Patient support groups have been founded worldwide (see www.debra.org.uk).

10.1.4 Current Established Therapies

Since no cure for EB and the other genetic skin blistering disorders exists, the current treatments are symptomatic. Patients with severe subtypes and multiorgan disease need multidisciplinary care.

10.1.4.1 Topical Medication

In all EB forms, appropriate skin care is indicated, and it consists of a high standard of personal hygiene and intensive moisturizing care. Simple blisters without secondary trauma or infection usually heal well with everyday skin care and disinfection. Modern aqueous disinfectants, e.g., octenidin-HCl, are highly effective and pleasant to use. Adhesives and compressive dressings must be avoided, since they induce new blisters. The wound should be covered with semi-occlusive nonadhesive dressings, which can be held in place with a sock, tubular bandage, or cotton bandage. Modern, silicon-based, slightly adherent wound care products have proven very useful, in particular, for “difficult” skin areas, such as elbows, shoulders, or the trunk. The process of wound healing may be impaired by multiple factors including foreign bodies, bacteria, nutritional deficiencies, tissue anoxia, and exogenous agents. All of these factors must be considered in patients with EB. Topical antibiotics should be avoided, until secondary infections are present. Fucidic acid, tetracycline, erythromycin, and clindamycin ointments have proven to be successful regimens. Creams supporting reepithelization are also useful. Topical corticosteroids can be used in cases of contact dermatitis or pruritus, only for short periods of time.

10.1.4.2 Systemic Therapy

Usually, no systemic therapy is required for EB. Tetracyclins were reported to reduce blistering in EBS [10], but this may be based on effects other than that of antibacteria. Systemic corticosteroids have been applied for short time periods in very severe cases of JEB Herlitz and EBS Dowling-Meara to reduce secondary inflammation, but high dosage may be required, and the side effect can be massive. Systemic antibiotics are indicated when systemic infections occur. In patients with the rare DEB with pruriginous lesions, cyclosporin and thalidomide have been reported to be effective [28, 40]. In severe forms of DEB, anemia is a frequent feature and must be treated appropriately; intravenous iron may be required. Because nutritional zinc deficiency may occur in some individuals, zinc substitution has been used to support wound healing in EB [4].
**10.1.4.3 Surgery**

Surgery is indicated for the curative treatment of pyloric atresia in EB with pyloric atresia. For solving complications of severe DEB: e.g., mitten-hand deformities, surgery and skin grafting can produce good results in separating the fingers, but often, the pseudosyndactylies recur within 1–2 years after surgery. Esophagus dilatation is often required, when strictures prevent swallowing and normal food intake. Skin grafting and cultured epidermal autografts have been partially successful in covering denuded areas in nonhealing wounds in DEB, or in JEB [21].

**10.1.4.4 Skin Cancer Screening**

Individuals with DEB have an increased risk of squamous cell carcinoma from early adolescence, and invasive aggressive squamous cell carcinoma is the cause of death in a high percentage of patients with severe DEB. Therefore, once- or twice-yearly skin cancer screening with clinical examination of the entire integument, biopsy of suspicious lesions, and patient education are pivotal preventive measures. Excisional surgery of the carcinoma is the therapy of choice, followed by regular clinical controls.

**10.1.4.5 Nutrition**

Oropharyngeal and gastrointestinal lesions threaten the nutritional well-being of patients with EB. Complications include oral blistering, abnormal esophageal motility, strictures, dysphagia, diarrhea, malabsorption, and dental problems. Nutritional assessment, taking these factors into account, is essential for replenishing the malnourished patient. High-caloric and protein-fortified foods and beverages may help replace protein lost in the fluid from draining blisters. Vitamin, mineral, and fiber supplements are often needed. The diet can be adjusted to prevent gastrointestinal problems, such as constipation, diarrhea, or painful elimination. Gastrostomy button insertion has been shown to be effective in providing adequate additional nutrition to individuals with esophageal strictures [14]. Remarkable improvement of a broad spectrum of symptoms, ranging from growth retardation to anemia and depression, has been achieved with additional feeding via gastrostomy button.

**10.1.4.6 Dental Care**

Good dental hygiene is essential for patients with EB, and regular visits to the dentist are recommended. Despite their best efforts, many patients with JEB and DEB develop dental caries because of enamel defects. In addition, significant oral mucosal involvement can accompany severe forms of JEB, DEB, and the KS. Harsh mouthwashes must be avoided and soft toothbrushes as well as rinsing with antiseptic solutions are indicated.

**10.1.4.7 Physical Therapy**

Inactivity as a result of pain and scarring can cause contractures to form. Physical therapy is helpful in reducing limb and hand contractions and in maintaining the range of motion. It is also indicated after surgery for mitten-hand deformity.

**10.1.4.8 Psychological Support**

In spite of enormous efforts and costs, the patients’ and their families’ life are marked by sustained suffering and sometimes hopelessness. Therefore, qualified psychological support and contacts with patient organizations are often helpful.

**10.1.4.9 Genetic Counseling**

Mutation analyses of EB candidate genes provide an immediate benefit to families of patients with EB, and affected families often request prenatal diagnosis. However, a prerequisite for this is that the defective gene and the mutation(s) of the index patient be disclosed. Preimplantation diagnosis has also been performed in EB cases [6].
10.1.5 Experimental Approaches

Currently, the treatment of EB is only symptomatic, and development of successful, curative molecular therapies is urgently needed. Although the routine clinical application of such treatments may still be years away, the rapid development of new technologies holds promise for individual biologically valid, evidence-based treatments. The design of such therapies is complicated by the fact that proteins of the DEJ have complex structures and aggregate into multimolecular suprastructures such as anchoring filaments, anchoring fibrils, or basement membrane layers.

A relatively broad spectrum of approaches to molecular therapies for different forms of EB has been considered [9, 18]. For dominant disorders, selective inhibition of gene expression by antisense strategy, mutation-specific ribozymes, or RNA-interference represents one way of treatment. Recent alternative concepts of supplementation therapies, based on the overexpression of the normal allele, or a natural alternatively spliced variant also hold promise. Further, structural reinforcement of the epidermal cells and their adhesion by additional proteins might be sufficient to compensate the negative effects of mutations and lead to clinical improvement [7]. For recessive DEB, protein, cell, and gene-based therapies have been tested in the animal model, and recently, in patients. Gene therapy with delivery of gene-corrected stem cells or vectors directing the expression of the missing protein will have the advantage of continuous production of collagen VII in the skin [8]. Retroviruses, lentiviruses, and nonviral transposon-mediated gene transfer techniques have been tested for transduction of keratinocytes in vitro; they successfully restored collagen VII or laminin 332 synthesis [3, 26, 27, 33]. Recently, the first human clinical trial using correction of JEB by transplantation of genetically modified epidermal stem cells was reported [22]. Epidermal stem cells from an adult patient with laminin-β3-deficient JEB were transduced with a retroviral vector expressing LAMB3 cDNA and used to prepare genetically corrected cultured epidermal grafts. Synthesis and proper assembly of normal levels of functional laminin 332 were observed, together with a firmly adherent epidermis that remained stable for the duration of at least 1 year follow-up [22]. Recent murine studies have shown that intradermal injections of allogeneic fibroblasts can lead to type VII collagen deposition and new anchoring fibrils at the DEJ [39]. Five individuals with recessive DEB were treated with a single intradermal injection of allogeneic fibroblasts, and an increase of type VII collagen expression for at least 3 months was achieved [37]. Protein therapy with direct intradermal injection of recombinant human collagen VII seems an attractive approach to treat DEB, because of its simplicity, and preliminary studies reported deposition of injected recombinant collagen VII at the DEJ in athymic mice carrying grafts of regenerated DEB skin [38]. Future research must show which of these promising experimental approaches will become suitable for effective and practical treatments of a large number of patients with EB.

10.1.6 Complications to Avoid

Infections are frequent complications of the chronic wounds and can be avoided by severe hygienic measures. Regular skin cancer screening is an important preventive measure for adults with DEB.

Take Home Message

- At present, the management of EB is mainly supportive and the therapy, symptomatic, because no specific cure exists. A high standard of personal hygiene and skin care, protection from trauma, and avoidance of infection are fundamental for optimal management.
- In many countries, specialized centers assure diagnosis and treatment for EB patients, and provide assistance for general practitioners, pediatricians, and dermatologists involved in management and care of EB.
- In the globalization era, worldwide collaborations are encouraged to offer improved diagnosis, support, and hope for future to as many patients and families as possible.
- Accurate molecular diagnosis and understanding of the disease mechanisms form the basis for design of novel, biologically valid therapeutic strategies.
- International networks of centers for research and patient care collaborate with the goal of developing cell-, protein-, or gene-based therapeutics for EB.
10.1.7 Global Variations

There are no known ethnic or gender predilections for EB.

Acknowledgment The authors’ work is supported by the German Network Epidermolysis bullosa and the EU Programs “Geneskin” and “Skintherapy.”

During compilation of this book, an international consensus conference agreed on a revised classification of EB, which kept the major EB categories, but eliminated some of the subtypes (Fine et al. J Am Acad. Dermatol 58:931-50, 2008). The new classification also included Kindler syndrome, the skin fragility-ectodermal dysplasia syndrome, the lethal acantholytic EB and the laryngo-oncho-cutaneous syndrome as new EB subtypes”.

References


10.2.1 Ichthyosis Vulgaris

10.2.1.1 Etiology and Pathophysiology

Ichthyosis vulgaris (IV) is caused by mutations in the keratin filament aggregating protein (filaggrin) gene [1]. IV is inherited as a semidominant trait; homozygotes have a severe phenotype, and heterozygotes have a mild phenotype. Filaggrin gene mutations are a major predisposing factor for atopic dermatitis as well [2]. The initial product of the filaggrin gene is profilaggrin, the main constituent of keratohyalin granules. Profilaggrin is proteolytically cleaved into multiple copies of filaggrin peptide. Filaggrin binds to and aggregates the keratin cytoskeleton, resulting in the flattening of the keratinocytes into squames. Filaggrin is also cross-linked into cornified cell envelopes to form the epidermal barrier. Loss or reduction of filaggrin leads to impaired keratinization. Breakdown products of filaggrin can retain water in the outer stratum corneum and their deficiency may also contribute to the scaling [3].

10.2.1.2 Clinical Characteristics and Diagnosis

IV presents within the first few months or years of life, with scaling of the skin that is generally pronounced on the extensor surfaces (Fig. 10.2.1). The scales are white, small, flaky, and semi-adherent. Hyperlinear palms and soles are seen in the majority of patients with IV. It is commonly associated with follicular hyperkeratosis and atopic dermatitis. Histologically, the affected skin shows mild hyperkeratosis and a diminished or absent granular layer in the epidermis. In males, clinical distinction from X-linked recessive ichthyosis may not be possible, and biochemical or genetic testing may be needed to differentiate it from IV.

10.2.1.3 General Therapeutic Outline

Applying topical emollient and avoiding low humidity environments are useful.

---

A. Ishida-Yamamoto
Department of Dermatology, Asahikawa Medical College,
Midorigaoka-Higashi 2-1-1-1, Asahikawa 078-8510, Japan
e-mail: akemi@asahikawa-med.ac.jp

Fig. 10.2.1 Ichthyosis
10.2.1.4 Current Established Therapies

Regular emollient application is recommended. Increasing environmental humidity at home is beneficial. Bath oils and a variety of emollient soap substitutes are useful. The primary limiting factor in the treatment of IV is the common concurrence of atopic dermatitis rendering the patient more vulnerable to irritant topical preparations.

10.2.1.5 Complications to Avoid

Atopic dermatitis.

Take Home Message

› IV is a common disease. Moisturizers are the mainstay of therapy.

10.2.1.6 Global Variations

IV occurs in as many as 1 in 250 individuals and may be underdiagnosed because it can be so mild that affected individuals may not come to medical attention, particularly in countries with high-humidity.

10.2.2 X-linked Recessive Ichthyosis

10.2.2.1 Etiology and Pathophysiology

X-linked recessive ichthyosis (XLI) is caused by a deficiency of the enzyme, steroid sulfatase (STS), and primarily affects males [4]. Heterozygous females are clinically unaffected. STS is responsible for hydrolysis of cholesterol sulfate to cholesterol in the epidermis. In patients with XLI, accumulation of cholesterol sulfate in the epidermis leads to barrier instability, and inhibits desmosomal degradation, thereby leading to corneocyte retention [5, 6].

10.2.2.2 Clinical Characteristics and Diagnosis

Patients present during the first few weeks of life with generalized desquamation of large, loosely-adherent, translucent scales. This phase is followed by the appearance of tightly-adherent, dark brown, polygonal scales that are distributed symmetrically on the preauricular areas of the cheeks, neck, lateral areas of the trunk, and extremities, with relative sparing of flexural surfaces [4]. Extracutaneous manifestations of XLI include corneal opacities that do not affect vision, cryptorchidism, and an increased risk of testicular cancer. Enzymatic analysis of STS activity in cultured cells (e.g., leukocytes) can confirm the diagnosis of XLI. Serum lipoprotein electrophoresis may also be helpful in establishing the diagnosis, because high levels of cholesterol sulfate increase the mobility of the β-fraction of low-density lipoproteins [4]. The differential diagnosis of XLI includes IV, as well as mild forms of lamellar ichthyosis. In cases with clinical overlap, biochemical or genetic testing is indicated.

10.2.2.3 General Therapeutic Outline

Regular use of emollient and keratolytic preparations helps to reduce severity.

10.2.2.4 Current Established Therapies

Regular use of emollient, keratolytic, and urea-containing preparations helps to reduce severity. In severe XLI, short or intermittent course of oral retinoid therapy may be considered. Topical application of retinoids can be helpful for severe areas [7].
10.2.2.5 Experimental Approaches

Cholesterol-containing emollients improve scaling abnormality [6]. Topical liarozole, a retinoic acid metabolism blocking agent, was effective in various forms of ichthyosis, including XLI [8].

10.2.2.6 Complications to Avoid

Testicular carcinoma.

10.2.2.7 Global Variations

As oral retinoids, etretinate has been replaced by acit-retin in the US and Europe, but etretinate is the only approved retinoid in Japan. As topical retinoids, tretinoin, tazarotene, and adapalene are available in the US and Europe, but not in Japan.

10.2.3 Autosomal Recessive Ichthyosis (Lamellar Ichthyosis, Nonbullous Congenital Ichthyosiform Erythroderma, and Harlequin Ichthyosis)

10.2.3.1 Etiology and Pathophysiology

Mutations in the genes encoding transglutaminase-1, two lipoxigenases (ALOXE3, ALOX12B), ABCA12, ichthyin, and CYP4F22 have been identified in this group of diseases [10–15]. These patients have reduced barrier function with increased transepidermal water loss values [16]. This barrier defect results in release of signals that stimulate proliferation and inflammation of the epidermis.

10.2.3.2 Clinical Characteristics and Diagnosis

Most of LI and NBCIE patients are born as collodion babies. After shedding of their membrane-like covering, generalized scaling is apparent. The scales of LI are plate-like, large, dark brown or gray, and firmly adherent. Those of NBCIE are fine, small, white or gray, and semi-adherent. Erythroderma is more intense in NBCIE than in LI. Additional features in some patients are palmo-plantar keratoderma, scarring alopecia, and ectropion. Infants affected with HI are covered with large, thick, yellow–brown, firmly adherent, dense hyperkeratotic plaques over the whole body surface, resulting in mitten-like deformities of hands and feet, as well as marked eversion of the lips and eyelids. Movement is restricted, and respiratory insufficiency results from limited chest expansion. Patients usually die at less than 1 week of age. Survivors develop severe ichthyosis resembling NBCIE. With regard to differential diagnosis of cases with an NBCIE phenotype, Netherton’s syndrome and neutral lipid storage disease must be considered.

10.2.3.3 General Therapeutic Outline

Systemic retinoids and topical emollients represent the current treatment options [17].

10.2.3.4 Current Established Therapies

Collodion babies should be nursed in a special care baby unit in a humidified incubator. An emollient, such

Take Home Message

› XLI is a clinically mild genetic disorder. Moisturizers and keratolytics are the mainstays of treatment.

Key Features

› A genetically heterogeneous group of autosomal recessive disorders, characterized by a congenital onset of generalized severe scaling [9]. Its clinical phenotypes include lamellar ichthyosis (LI), nonbullous congenital ichthyosiform erythroderma (NBCIE), and Harlequin ichthyosis (HI).
as sterile white soft paraffin is usually applied every 4 h to reduce transepidermal water loss. Signs of cutaneous or systemic infections should be investigated and treated immediately. HI babies need intensive care to cope with the predictable problems of hypothermia, feeding and respiratory difficulties, dehydration, electrolyte and renal complications, and sepsis. Early introduction of systemic retinoids in the newborn period of HI can be life-saving [18]. For older patients with autosomal recessive ichthyosis, the use of emollients remains a cornerstone of treatment. Topical retinoids [7, 19] and vitamin D₃ derivatives [20] may also be helpful; however, the increased skin permeability of the patient may result in toxicity by cutaneous absorption of substances applied to the skin. Systemic toxic effects of salicylate and lactic acid have been reported in patients with LI after topical application [21, 22]. High plasma urea levels have also been reported in IL patients treated with products containing urea [23, 24]. Oral retinoids are particularly effective in reducing the amount of scales, but this may expose underlying erythroderma. Considerable adverse effects, e.g., teratogenicity, hepatotoxicity, and hyperostosis, are limiting factors with this therapy. Those with ectropion should receive ophthalmologic care. Genetic counseling and the availability of prenatal diagnosis must be made known to parents.

10.2.3.5 Experimental Approaches

Topical application of the antioxidant N-acetylcysteine was reported to result in marked improvement in a patient with LI [25]. An LI patient treated with 0.1% tacrolimus had significant drug absorption that correlated with marked clinical improvement [26]. Topical liarozole, a retinoic acid metabolism blocking agent, was effective in various forms of ichthyosis, including LI [8]. LI has been studied as a prototype for therapeutic cutaneous gene delivery. Restoration of transglutaminase activity in keratinocytes from LI patients has been shown to normalize protein cross-linking and cornification in vitro and in a human skin/immunodeficient mouse xenograft model [27, 28]. It has been reported that ABCA12 defects caused congested lipid secretion in cultured HI keratinocytes, and lipid secretion was recovered after corrective gene transfer of ABCA12 into cultured keratinocytes [10]. Topical cutaneous N-acetylcysteine was reported to be useful in the treatment of major bilateral ectropion in an infant with LI [29].

10.2.3.6 Complications to Avoid

Sepsis, dehydration, and percutaneous poisoning.

**Take Home Message**

- Treatment is directed at decreasing symptoms.

10.2.3.7 Global Variations

As oral retinoids, etretinate has been replaced by acitretin in the US and Europe, but etretinate is the only approved retinoid in Japan. As topical retinoids, tretinoin, tazarotene, and adapalene are available in the US and Europe, but not in Japan. As topical Vitamin D₃ derivatives, tacalcitol, calcipotriol, and maxacalcitol are used in Japan. Tacalcitol is used in Europe, and calcipotriol is used in the US and Europe, as well.

10.2.4 Bullous Congenital Ichthyosiform Erythroderma

**Key Feature**

- Generalized hyperkeratosis and epidermal fragility.

10.2.4.1 Etiology and Pathophysiology

Bullous congenital ichthyosiform erythroderma (BCIE) is a rare autosomal dominant genodermatosis, caused by mutations in the gene encoding the epidermal intermediate filament proteins keratin 1 and keratin 10. The expression of the mutant gene product interferes with the function of the normal gene product
10.2 Inherited Keratinocyte Diseases (Ichthyosis and Related Disorders)

565

(dominant negative effects). Abnormal keratin network results in epidermal fragility. The mechanisms underlying the hyperkeratosis are not fully understood.

10.2.4.2 Clinical Characteristics and Diagnosis

BCIE presents at birth with generalized erythema, blisters and erosions. In the subsequent months after birth, erythema and blistering improve but patients go on to develop generalized hyperkeratotic scaling. Skin biopsy shows diagnostic features of epidermolytic hyperkeratosis. The widespread blistering and erosions seen in neonates with BCIE must be differentiated from other blistering diseases, including staphylococcal scalded skin syndrome and epidermolysis bullosa. Mild cases of BCIE must be differentiated from Ichthyosis Bullosa of Siemens, which is caused by a keratin 2e mutation.

10.2.4.3 General Therapeutic Outline

Emollients are useful in the neonatal period. Keratolytic preparations and oral retinoid therapy may improve hyperkeratosis.

10.2.4.4 Current Established Therapies

Neonates with BCIE require management in an intensive care nursery. Exposure to a high-humidity environment and frequent use of topical petrolatum-based emollients are helpful to prevent excessive fluid loss. For the treatment of hyperkeratosis in older patients, keratolytic preparations, such as salicylic acid, urea or alpha-hydroxy acid containing creams, topical retinoids, and vitamin D$_3$ derivatives, may be helpful [20, 30]. Oral retinoid therapy may be beneficial, but may increase skin fragility, blistering, and tenderness [31]. Regular use of antiseptic washes and appropriate systemic antibiotics may be required in cases with repeated cutaneous bacterial and fungal infection and associated body odor.

10.2.4.5 Experimental Approaches

Topical liarozole, a retinoic acid metabolism blocking agent, was effective in various forms of ichthyosis, including BCIE [8]. Prenatal diagnosis can be carried out by DNA testing on cells collected by chorionic villus sampling or amniocentesis [32].

10.2.4.6 Complications to Avoid

In the newborn period, management of dehydration and secondary infection is important.

Take Home Message

- There is a strong association between keratin 1 mutations and palmoplantar keratoderma [31]. Retinoid therapy is particularly effective in patients with keratin 10 mutations [31].

10.2.4.7 Global Variations

See autosomal recessive ichthyosis.

10.2.5 Netherton’s Syndrome

10.2.5.1 Etiology and Pathophysiology

Netherton’s syndrome (NS) is caused by mutations in the SPINK5 gene resulting in a lack of the serine protease inhibitor LEKTI and dysregulation of epidermal proteolysis [33].
10.2.5.2 Clinical Characteristics and Diagnosis

NS is an autosomal recessive condition characterized by the triad of congenital ichthyosiform erythroderma or ichthyosis linearis circumflexa, trichorrhexis invaginata or other hair shaft anomalies, and atopic features. Diagnosis is typically delayed because of the gradual evolution and heterogeneity of clinical features. Differential diagnosis includes NBCIE, Omenn’s syndrome, and atopic dermatitis.

10.2.5.3 General Therapeutic Outline

Topical emollients. Topical or systemic antibiotics for skin and respiratory infections.

10.2.5.4 Current Established Therapies

In the neonatal period, intensive medical, nursing, and nutritional care must be available to treat erythroderma, systemic infection, hypernatraemic dehydration and failure to thrive, if they occur. Regular use of topical emollients, such as paraffin mixture and ammonium lactate lotion, is effective [34]. Oral retinoids are not typically beneficial. Topical corticosteroids are ineffective.

10.2.5.5 Experimental Approaches

Phototherapies with broadband UVB, PUVA, and UVA1 have been reported as effective treatments for NS [35]. Topical intermittent therapy with small amounts of tacrolimus was reported to be effective for NS [36], but significant absorption due to the impaired epidermal barrier has been reported [37]. Successful treatment with topical pimecrolimus, without serious side-effects and without developing significant systemic absorption of pimecrolimus has been reported [38]. The effectiveness of topical vitamin D₃ derivatives has also been reported [39]. A clinical trial of a topical protease inhibitor is underway [40].

10.2.5.6 Complications to Avoid

Cutaneous and systemic infections.

Take Home Message

Management is conservative. Emollients are the mainstay of treatment in NS.

10.2.5.7 Global Variations

Topical tacrolimus is contraindicated or not recommended in patients with NS in the US, Europe and Japan.

10.2.6 Sjögren-Larsson syndrome

10.2.6.1 Etiology and Pathophysiology

Sjögren-Larsson syndrome (SLS) is caused by a deficiency of fatty aldehyde dehydrogenase (FALDH), encoded by the ALDH3A2 gene. FALDH catalyzes the oxidation of different long- and medium-chain fatty aldehydes to fatty acids. The resulting tissue accumulation of free fatty alcohol, fatty aldehyde, and related lipid metabolites is thought to be responsible for the clinical symptoms.

10.2.6.2 Clinical Characteristics and Diagnosis

SLS is an autosomal recessive neurocutaneous disorder characterized by the clinical symptom of triad of generalized ichthyosis, mental retardation, and spastic...
diplegia or tetraplegia. The ichthyosis is usually apparent at the time of birth. A velvety orange or brown lichenification is usually generalized, but most obvious in the flexures, neck and abdomen. Patients also suffer from severe pruritus. In most cases, neurological symptoms develop within the first 3 years of life, along with a developmental delay in motor and cognitive functions. Spasticity leads to progressive contractures, preventing or impairing the ability to walk in most patients. Most patients have an IQ of less than 50. Essentially, all patients develop juvenile macular dystrophy of the retina, manifesting as a glistening white spot.

### 10.2.6.3 General Therapeutic Outline

Treatment options are primarily symptomatic.

### 10.2.6.4 Current Established Therapies

Treatment of the skin lesions with topical emollients, keratolytic agents, or vitamin D₃ derivative is useful. Oral retinoid therapy is effective in relieving the scaling and lichenification. Orthopedic or surgical treatment of the joint contractures and genetic advice are also important.

### 10.2.6.5 Experimental Approaches

Therapeutic responses to dietary manipulation have been inconsistent [41]. The degradation of leukotriene B₄ is impaired in SLS, and some favorable clinical effects of a leukotriene B₄ synthesis inhibitor, zileuton, were reported [42]. A hypolipidemic drug, bezafibrate was shown to induce FALDH activity in fibroblasts of control subjects and SLS patients who still have some residual FALDH activity [43]. Introduction of functional FALDH gene into defective SLS cells resulted in an augmentation of FALDH activity and supported the concept of gene therapy as a potential future treatment option for SLS [44].

### 10.2.6.6 Complications to Avoid

Flexion contractures of joints and epileptic seizures.

### Take Home Message

- SLS is a multisystem disease and requires the attention of many specialists, including dermatologists, neurologists, pediatricians, physiotherapists, ophthalmologists, and orthopedists.

### 10.2.6.7 Global Variations

As oral retinoids, etretinate has been replaced by acitretin in the US and Europe, but etretinate is the only approved retinoid in Japan. As topical Vitamin D₃ derivatives, tacalcitol, calcipotriol, and maxacalcitol are used in Japan. Tacalcitol is used in Europe, and calcipotriol is used in the US and Europe, as well.

### 10.2.7 Darier’s Disease

#### 10.2.7.1 Etiology and Pathophysiology

Darier’s disease is caused by mutations in the gene encoding a sarco/endoplasmic reticulum calcium ATPase pump (SERCA2) [45].

#### 10.2.7.2 Clinical Characteristics and Diagnosis

The distinctive lesion of Darier’s disease is a firm, greasy, crusted, coalescent, yellow–brown papule [46].
These lesions usually appear between the ages of 6 and 20 years. Coalescence of the papules produces irregular warty plaques in the central trunk, the neck, the forehead, the ears, and the scalp. Painful blistering may be caused by infection with either *Staphylococcus aureus* or herpes simplex virus. The histology shows acantholytic dyskeratosis.

### 10.2.7.3 General Therapeutic Outline

Emollients and oral retinoids [46].

### 10.2.7.4 Current Established Therapies

Topical emollients are useful. Topical retinoids have been reported as effective [47]. The skin lesions usually respond to oral retinoids. Oral antibiotics may prevent secondary infection.

### 10.2.7.5 Complications to Avoid

Bacterial and viral infections.

### 10.2.7.6 Global Variations

As oral retinoids used for the treatment of Darier’s disease, acitretin and isotretinoin (13-cis retinoic acid) are used in the US and Europe, but these are not available in Japan and etretinate is the only approved retinoid in this country. As topical retinoids, tretinoin, tazarotene, and adapalene are available in the US and Europe, but not in Japan.

### 10.2.8 Palmoplanter Keratoderma

#### Key Features

- Hyperkeratosis predominantly affecting the palms and soles.

#### 10.2.8.1 Etiology and Pathophysiology

Palmoplanter keratoderma (PPK) is a large and heterogeneous group of disorders with different etiology and pathophysiology (Table 10.2.1) [48, 49].

#### 10.2.8.2 Clinical Characteristics and Diagnosis

This is a clinically diverse group of diseases defined by gross hyperkeratosis of palms and soles [48, 49]. Some are diffuse and others have discrete, corn-like hardening. Some have additional features in nonglabrous skin, or abnormalities in other organs.

#### 10.2.8.3 General Therapeutic Outline

General Therapeutic Outline. Application of topical keratolytics.

#### 10.2.8.4 Current Established Therapies

Emollients, keratolytics, and vitamin D₃ derivative may be used. Oral retinoids may be effective for some patients. Surgical excision of the keratotic masses is sometimes useful. A low phenylalanine and tyrosine diet improves the eye and skin lesions in the patients with Richner-Hanhart syndrome caused by tyrosine aminotransferase deficiency, and prevents mental retardation if the diet is established early enough in childhood.

### Take Home Message

- Cool cotton clothing and sun block creams should reduce exacerbation in summer [46].
Table 10.2.1 Palmoplantar keratoderma (PPK)

<table>
<thead>
<tr>
<th>Type (OMIM entry)</th>
<th>Inheritance</th>
<th>Causative gene (linkage)</th>
<th>Onset of PPK (year)</th>
<th>Nature of PPK</th>
<th>Other symptoms of hands and feet</th>
<th>Other muco-cutaneous lesions</th>
<th>Other symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple PPK (only the skin is involved)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unna-Thost, nonepidermolytic PPK (600962)</td>
<td>AD</td>
<td>K1</td>
<td>Soon after birth</td>
<td>Diffuse, with a sharp demarcation and erythematous edge</td>
<td>Hyperhidrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vörner, Epidermolytic PPK (144200)</td>
<td>AD</td>
<td>K9, K1</td>
<td>(0–3)</td>
<td>Diffuse, with a sharp demarcation and erythematous edge, epidermolytic hyperkeratosis on biopsy</td>
<td>Blistering</td>
<td>Knuckle pads, nail changes</td>
<td></td>
</tr>
<tr>
<td>Sybert</td>
<td>AD</td>
<td>Unknown</td>
<td>Infancy</td>
<td>Diffuse</td>
<td>Glove and stocking distribution, autoamputaion of toes</td>
<td>Hyperkeratosis on the elbows, knees, groins and natal cleft</td>
<td></td>
</tr>
<tr>
<td>Greither</td>
<td>AD</td>
<td>(1q36.2-34)</td>
<td>(8–10) Regression by 60 years</td>
<td>Diffuse</td>
<td>Glove and stocking distribution, hyperhidrosis</td>
<td>Patchy lesions of knees and elbows</td>
<td></td>
</tr>
<tr>
<td>Mal de Meleda (248300)</td>
<td>AR</td>
<td>SLURP-1</td>
<td>(0–3)</td>
<td>Diffuse, waxy ivory-yellow hyperkeratosis</td>
<td>Hyperkeratosis extends to the back of hands and feet, sclerodactyly, digital constrictions, hyperhidrosis</td>
<td>Hyperkeratosis on the knees and elbows, perioral erythema, nail changes</td>
<td></td>
</tr>
<tr>
<td>Gamborg-Nielsen (244850)</td>
<td>AR</td>
<td>unknown</td>
<td>(2–3)</td>
<td>Diffuse</td>
<td>Hyperkeratosis extends to the back of hands and feet, digital constrictions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loricrin keratoderma (604117)</td>
<td>AD</td>
<td>Loricrin</td>
<td>Infancy</td>
<td>Diffuse, waxy, honeycomb appearance, diffuse edge</td>
<td>Constrictions of the digits</td>
<td>Ichthyosis</td>
<td></td>
</tr>
<tr>
<td>Huriez, Sclerothylosis (%181600)</td>
<td>AD</td>
<td>(4q23-q31)</td>
<td>Congenital</td>
<td>Diffuse</td>
<td>Atrophic fibrosis</td>
<td>Skin cancer, nail hypoplasia</td>
<td>Internal malignancy?</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Type (OMIM entry)</th>
<th>Inheritance</th>
<th>Causative gene (linkage)</th>
<th>Onset of PPK (year)</th>
<th>Nature of PPK</th>
<th>Other symptoms of hands and feet</th>
<th>Other muco-cutaneous lesions</th>
<th>Other symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olmsted syndrome</td>
<td>AD?</td>
<td>Unknown</td>
<td>(0–2)</td>
<td>Diffuse</td>
<td>Spontaneous amputation of the digits</td>
<td>Periorificial keratotic plaques, flexion deformity of fingers</td>
<td>–</td>
</tr>
<tr>
<td>Pachyonychia congenital (167200, 167210) Focal PPK</td>
<td>AD</td>
<td>K6a, K6b, K16, K17</td>
<td>Infancy</td>
<td>Focal</td>
<td>Onychogryposis, steatocystoma, Oral leukokeratosis</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Type I striate PPK (#148700)</td>
<td>AD</td>
<td>Desmoglein 1,</td>
<td>Infancy–puberty</td>
<td>Striate, over the pressure point</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type II striate PPK (+125647.0001)</td>
<td>AD</td>
<td>Desmoplakin</td>
<td>The first or early second decade</td>
<td>Striate, over the pressure point</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex PPK (other organs are involved as well)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carvajal syndrome (605676) (+125647.0002)</td>
<td>AR</td>
<td>Desmoplakin</td>
<td>Around the first year</td>
<td>Striate</td>
<td>Wooly hair</td>
<td>Left ventricular cardiomyopathy</td>
<td></td>
</tr>
<tr>
<td>Arrhythmogenic right ventricular cardiomyopathy with PPK and wooly hair</td>
<td>AR</td>
<td>Desmocollin 2</td>
<td></td>
<td></td>
<td>Wooly hair</td>
<td>Arrhythmogenic right ventricular cardiomyopathy [50]</td>
<td></td>
</tr>
<tr>
<td>Naxos disease (601214)</td>
<td>AR</td>
<td>Plakoglobin</td>
<td>(1–)</td>
<td>Diffuse</td>
<td>Wooly hair</td>
<td>Arrhythmia, right ventricular cardiomyopathy, sudden death</td>
<td></td>
</tr>
<tr>
<td>Papillon-Lefèvre syndrome (#245000), Haim-Munk syndrome (#245010)</td>
<td>AR</td>
<td>Cathepsin C</td>
<td>(–3)</td>
<td>Diffuse</td>
<td>Hyperhidrosis</td>
<td>Keratosis on the elbows and knees, onychogryposis</td>
<td>Periodontitis, premature tooth loss, arachnodactyly, recurrent pyogenic skin infections</td>
</tr>
<tr>
<td>Bureau-Barriere-Thomas syndrome, Acro-osteolysis with keratoderma</td>
<td>AR</td>
<td>Unknown</td>
<td>Childhood</td>
<td>Diffuse</td>
<td>Finger clubbing, hyperhidrosis</td>
<td>Foot ulcer</td>
<td>Osteolysis, polyneuropathy</td>
</tr>
<tr>
<td>Inherited Keratinocyte Diseases (Ichthyosis and Related Disorders)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vohwinkel syndrome</strong>&lt;br&gt; (124500)</td>
<td>AD</td>
<td>GJB2 Connexin 26</td>
<td>Infancy</td>
<td>Diffuse, waxy, honeycomb appearance</td>
<td>Constrictions of the digits</td>
<td>Starfish extensor keratoses</td>
<td>Hearing loss, mild to moderate</td>
</tr>
<tr>
<td><strong>Mitochondrial hearing loss with PPK</strong>&lt;br&gt; (590080.0002)</td>
<td>Mito</td>
<td>Mitochondrial tRNA ser(UCN)</td>
<td>Childhood–young adult</td>
<td>Focal, Diffuse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Schröpf-Schulz-Passage syndrome</strong>&lt;br&gt; (%224750)</td>
<td>AR</td>
<td>WNT10A</td>
<td>Puberty</td>
<td>Diffuse</td>
<td>Eyelid cysts, hypotrichosis, hypoplastic nails</td>
<td>Hypodontia</td>
<td></td>
</tr>
<tr>
<td><strong>Naegeli-Franceschetti-Jadassohn syndrome</strong>&lt;br&gt; (161000)</td>
<td>AD</td>
<td>K14</td>
<td>Childhood</td>
<td>Diffuse and punctate</td>
<td>Absent finger print, hypohidrosis</td>
<td>Reticulate hyperpigmentation</td>
<td>Premature tooth loss</td>
</tr>
<tr>
<td><strong>Howel-Evans syndrome</strong>&lt;br&gt; (%148500)</td>
<td>AD</td>
<td>(17q25)</td>
<td>(7–8)</td>
<td>Focal, over pressure points</td>
<td>Bucal mucosal leukoplakia, follicular keratosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Richner-Hanhart syndrome</strong>&lt;br&gt; (+276600)</td>
<td>AR</td>
<td>Tyrosine amino transferase</td>
<td>Infancy</td>
<td>Focal</td>
<td>Painful</td>
<td>Herpetiform corneal ulcers, mental retardation</td>
<td></td>
</tr>
<tr>
<td><strong>Clouston syndrome, Hydrotic ectodermal dysplasia</strong>&lt;br&gt; (129500)</td>
<td>AD</td>
<td>GJB6 Connexin 30</td>
<td>Diffuse</td>
<td></td>
<td>Hyperpigmentation, onychodystrophy, alopecia</td>
<td>Short stature, cataract, photophobia, strabismus, conjunctivitis, blepharitis</td>
<td></td>
</tr>
<tr>
<td><strong>Occulodentodigital dysplasia with PPK</strong>&lt;br&gt; (#164200)</td>
<td>AD</td>
<td>GJA1 Connexin 43</td>
<td>Diffuse, yellow–orange</td>
<td></td>
<td></td>
<td>Ocular anomalies, finger and toe syndactyly, enamel defects</td>
<td></td>
</tr>
</tbody>
</table>

*AD* autosomal dominant; *AR* autosomal recessive; *Mito* mitochondrial; *OMIM* online Mendelian Inheritance In Man;


10.2.8.5 Complications to Avoid

Dermatophyte infection.

Take Home Message

- The differentiation of the simple PPKs, in which only the skin is involved, from those which have associated features such as deafness, periodontitis, cardiomyopathy, and esophageal carcinoma is important.

10.2.8.6 Global Variations

See Sjögren–Larsson syndrome.

References

10.3.1 Chronic Mucocutaneous Candidiasis (CMC)

Key Features

- Recurrent and progressive candidal infections of skin, nails and mucosae
- May be associated with autoimmune endocrinopathies

10.3.1.1 Etiology and Pathophysiology

Patients show immunodeficiency with shared inability to respond to *C. albicans*. Humoral immunity usually appears normal and up to 35% of patients have no apparent immunologic defects or family history. Those with affected relatives may have candidiasis endocrinopathy syndrome (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome, APECED) which results from a mutation in AIRE (autoimmune regulator gene) [6].

10.3.1.2 Clinical Characteristics and Diagnosis

Patients have recurrent, progressive infections of the skin, nails, and mucous membranes due to *C. albicans*. Depending on subtype, the clinical presentation ranges from recurrent, recalcitrant thrush and mild erythematous scaling plaques with a few dystrophic nails to severe generalized, crusted granulomatous plaques. Patients rarely develop systemic candidiasis but 50% may develop recurrent or severe infections due to other organisms.

10.3.1.3 General Therapeutic Outline

Systemic treatment of candidal infections is indicated.

10.3.1.4 Current Established Therapies

Candidal lesions generally respond to oral azole antifungal agents (itraconazole, fluconazole) or terbinafine. Patients who are resistant usually respond to amphotericin B with or without flucytosine. Abnormal cell-mediated immunity is not normalized by drug therapy.

10.3.1.5 Experimental Approaches

Hematopoietic stem cell transplantation, fetal thymus grafts, and leukocyte infusions have been used in...
patients with severe immunologic deficiencies. Azole-resistant CMC has also been treated with caspofungin [15] or with micafungin [35]. Oral cimetidine with oral zinc sulfate has also been used with a reported positive outcome, including increased CD4 cell counts [23].

10.3.1.6 Complications to Avoid

Patients do not respond well to standard topical medications, and the cutaneous granulomas are especially difficult to treat.

Take Home Message

› CMC may be the first clue to autoimmune endocrinopathy, most commonly involving adrenal and parathyroid glands.

10.3.1.7 Global Variations

Despite the greater risk for hepatotoxicity, and perhaps due to economic consideration, oral ketoconazole is considered as an alternative therapy in some geographic areas.

10.3.2 Cartilage-Hair Hypoplasia Syndrome (CHHS)

10.3.2.1 Etiology and Pathophysiology

The disorder results from mutations in RMRP, the RNA component of a ribonucleoprotein endoribonuclease [27].

10.3.2.2 Clinical Characteristics and Diagnosis

Chronic oral fungal or viral infections as well as recurrent upper respiratory tract infections, otitis media, and pneumonias are related to defective cellular and humoral immunity. Patients have fine, sparse, hypopigmented hair and metaphyseal dysostosis that results in short-limbed dwarfism. Patients may have soft, doughy skin with degenerated elastic tissue.

10.3.2.3 General Therapeutic Outline

Supportive therapy with appropriate antibiotic, antiviral, and antifungal treatment is indicated.

10.3.2.4 Experimental Approaches

Bone marrow transplantation, although rarely performed, fully corrects the immune deficiency but has no influence on the course of the chondroplasia or on elastic tissue.

Take Home Message

› Sparse hair and bony abnormalities allow early recognition of associated immunodeficiency.

10.3.2.5 Global Variations

Internationally, treatment strategies are similar.
10.3.3 Severe Combined Immunodeficiency

Key Features

- Heterogeneous group of autosomal recessive or X-linked recessive disorders
- Severely impaired humoral and cellular immunity with deficiencies of T, B, and/or NK cells
- Recurrent infections, diarrhea, and failure to thrive within the first 6 months of life

10.3.3.1 Etiology and Pathophysiology

X-linked SCID affects approximately 46% of patients [4] and the genetic defect is a mutation in \( \gamma \) chain of the interleukin 2 (IL-2) receptor. The most common form of autosomal recessive SCID (16% of patients) results from mutations in the gene for the purine-degradation enzyme adenosine deaminase (ADA).

10.3.3.2 Clinical Characteristics and Diagnosis

Infants show recurrent sinopulmonary and skin infections within the first months of life and fail to gain weight. Persistent mucocutaneous candidiasis is often present at the time of diagnosis, and systemic candidal infections occur occasionally. Viral infections tend to be fatal. The most common cutaneous eruptions are morbilliform or show generalized erythroderma and may be difficult to distinguish from GVHD, which may also result from in utero transfer of maternal cells. Affected children with most forms of SCID rarely survive beyond 1 year of age without transplantation.

10.3.3.3 Current Established Therapies

The definitive treatment of choice for SCID is a hematopoietic stem cell transplant from HLA-identical or haploidentical T-cell depleted bone marrow [24]. Bone marrow transplants done before the age of 3 months have a 95% survival rate whereas after 3 months of age the survival rate decreases to 75%.

10.3.3.4 Experimental Approaches

Gene therapy is currently restricted to patients who are unlikely to survive allogenic transplantation or who have undergone unsuccessful transplantation. Patients with IL-2 deficiency have been treated with IL-2 injections. Enzyme replacement therapy with polyethylene glycol modified bovine ADA, administered subcutaneously once weekly, has resulted in clinical and immunologic improvement in patients with ADA deficiency.

10.3.3.5 Complications to Avoid

Transplantation or exposure to unirradiated transfused cells may result in GVHD.

Take Home Message

- Infants with recalcitrant generalized erythroderma or dermatitis who show early infections and failure to thrive should be referred for immunologic evaluation and early transplantation as appropriate.

10.3.3.6 Global Variations

Internationally, treatment strategies are similar.

10.3.4 Hypohidrotic Ectodermal Dysplasia with Immunodeficiency (HED-ID)

Key Features

- Characteristic facies of HED
- Severe ID with infections early in infancy
- Occurs in boys
10.3.4.1 Etiology and Pathophysiology

HED-ID results from hypomorphic mutations in the NEMO (NF-κB essential modulator) gene, which is on the X chromosome. NF-κB is also shown to transduce signaling via ectodysplasin. Carrier mother may show features of incontinentia pigmenti. NEMO is required for NF-κB activation.

10.3.4.2 Clinical Characteristics and Diagnosis

Presents with classic features of HED including hypotrichosis or atrichia, hypohidrosis (leading to heat intolerance), hypodontia or anodontia with conical incisors, and associated dermatitis [20, 25].

10.3.4.3 Current Established Therapies

Transplantation is the treatment of choice. Ectodermal dysplasia is treated supportively. Patients with impaired antibody production may benefit from IVIG. All infections (bacterial and viral) should be treated aggressively. Prophylaxis for both P. carinii and M. avium intracellulare should be considered.

10.3.4.4 Complications to Avoid

It is unlikely that successful treatment reverses the ectodermal dysplasia, so that management of hypohidrosis is critical in survivors.

Take Home Message

› Recognize the possibility that infant boys with facial features of HED have this form of ID.

10.3.4.5 Global Variations

Internationally, treatment strategies are similar.

10.3.5 Ataxia-Telangiectasia (AT)

10.3.5.1 Etiology and Pathophysiology

AT results from mutations in the ataxia-telangiectasia mutated (ATM) gene, which encodes a phosphatidylinositol 3-kinase-like serine/threonine protein kinase that plays a central role in activating apoptotic and cell cycle responses to DNA damage [33].

10.3.5.2 Clinical Characteristics and Diagnosis

Characteristic oculocutaneous telangiectases begin near the ocular canthi and progress across the bulbar conjunctivae. Progeric changes of the skin, including xerosis and gray hair, occur in 90% of patients. During adolescence, the facial skin may become progressively atrophic and sclerotic, causing a masklike appearance. Recalcitrant noninfectious cutaneous granulomas are problematic for many patients. The progressive cerebellar ataxia first becomes apparent during infancy, often years before skin or conjunctival abnormalities develop.

10.3.5.3 Current Established Therapies

Therapy is supportive: antibiotics for infections and possibly IVIG therapy; intralesional triamcinolone injections for granulomas (after tissue cultures yield no organisms); avoidance of sun exposure and use of sunscreens; early
physiotherapy for patients with pulmonary bronchiectasis and consideration of systemic corticosteroid therapy for interstitial lung disease; physical therapy for patients with neurologic dysfunction; aggressive screening for development of malignancy.

### 10.3.5.4 Experimental Approaches

In a small subset of patients, treatment with aminoglycosides increased ATM gene function [16]. Iron chelators have been shown to increase the resistance of AT cells to oxidative stress [32]. Systemic corticoid therapy has also been reported to improve neurologic symptoms [5].

### 10.3.5.5 Complications to Avoid

The development of telangiectasia may relate, at least in part, to the sensitivity to ultraviolet light of some AT strains. If malignancy occurs, chemotherapy is necessary; radiation and radiomimetic chemotherapeutic agents, especially bleomycin, should be avoided because of extensive tissue necrosis.

#### Take Home Message

- Ocular and facial telangiectasia may be the diagnostic clue to the cause of ataxia and the association of immunodeficiency.

### 10.3.5.6 Global Variations

Internationally, treatment strategies are similar.

### 10.3.6 Antibody Deficiencies Disorders

#### Key Features

- Common variable immunodeficiency (CVID) is a heterogeneous disorder characterized by low levels of most immunoglobulin classes with recurrent pulmonary infections and no evidence of antibodies to bacterial antigens.
- Hyper-IgM syndrome is usually X-linked recessive and is characterized by low or no IgG, IgE, and IgA levels, with normal levels of IgM and IgD with an increased susceptibility to apthous ulcers and warts, in addition to other infections.

#### 10.3.6.1 Etiology and Pathophysiology

The underlying defect in XLA is failure of maturation of the pre-B cell to a differentiating B cell. The causative gene, Btk (Bruton’s or B-cell tyrosine kinase) participates in B-cell receptor intracellular signaling and B-cell maturation.

Identified genetic defects underlying CVID include defects in TACI (transmembrane activator-most common, calcium modulator, and cyclophilin ligand interactor), ICOS (inducible costimulator), BAFF-R (B-cell activation factor of the tumor necrosis factor family receptor) and CD19. Each of these is critical for B-lymphocyte activation and differentiation.

Hyper-IgM syndrome, an X-linked or autosomal recessive disorder, is caused by a defect of B cell differentiation [38]. B cells respond to antigen, but produce only IgM antibodies.

#### 10.3.6.2 Clinical Characteristics and Diagnosis

XLA is characterized by recurrent pyogenic infections, beginning when maternal antibodies disappear at approximately 9 months of age. Skin infections, especially furunculosis and impetigo, an atopic-like dermatitis, pyoderma gangrenosum, and noninfectious cutaneous granulomas have all been reported. Patients also show an increased predilection to enteroviral infections and lymphoproliferative malignancy.
Patients with CVID have infections similar to those in patients with XLA, particularly sinopulmonary infections, but are less susceptible to enteroviral infections. Autoimmune disorders are especially frequent [36]. The incidence of lymphoreticular malignancy and gastric carcinoma are markedly increased.

Patients with hyper-IgM syndrome tend to have recurrent respiratory tract infections as well as dermatitis, an increased incidence and severity of warts, and oral ulcerations, sometimes in association with neutropenia. Recurrent diarrhea, CNS infections, and sepsis are also common and there is an increased risk of gastrointestinal cancer.

### 10.3.6.3 Current Established Therapies

Periodic IVIG administration is standard treatment for immunoglobulin deficiency disorders. Prophylactic antibiotics should be initiated in patients who continue to have infections despite IVIG therapy [37].

In hyper-IgM syndrome, patients with autoimmune neutropenia may also respond to granulocyte-macrophage colony-stimulation factor (GMCSF). More than half of patients benefit from prophylactic antibiotics for *P. carinii*.

### 10.3.6.4 Experimental Approaches

Allogeneic bone marrow transplantation may correct these disorders, but it is limited to severe cases.

### 10.3.6.5 Complications to Avoid

Patients with XLA have developed paralysis after administration of live polio vaccine.

### 10.3.6.6 Global Variations

Internationally, treatment strategies are similar.

### 10.3.7 Wiskott-Aldrich Syndrome (WAS)

#### Key Features

- X-linked recessive immunodeficiency disorder characterized (when fully manifested) by the classic triad of atopic-like dermatitis, a bleeding tendency due to microthrombocytopenia, and recurrent sinopulmonary infections.
- Onset of bacterial infections in infancy, with later development of viral and *Pneumocystis* infections.
- Hepatosplenomegaly, lymphadenopathy, and autoimmune disease.
- Lymphomas occur in approximately 25% of survivors.

#### Etiology and Pathophysiology

The defective gene encodes WASp, a hematopoietic-specific cytoplasmic protein that functions in signaling and cytoskeletal organization. Mutations in WASp affect organization of the immunological synapse and T-cell activation, T and B lymphocyte migration, and initiation of the primary antibody response.

#### Clinical Characteristics and Diagnosis

The classic triad of WAS is hemorrhage due to persistent thrombocytopenia (<70,000 platelets) and platelet dysfunction, recurrent pyogenic infections, and calcific dermatitis; but this triad appears only in 25% of patients [21]. Nearly 40% of patients develop an autoimmune disorder [31], particularly vasculitis, autoimmune hemolytic anemia, and nephropathy.
10.3.7.3 General Therapeutic Outline

Therapeutic interventions allow some patients to survive into adulthood; however a significant proportion die before the age of 10 years secondary to hemorrhage, infection, malignancies or the complications of transplantation [7].

10.3.7.4 Current Established Therapies

Bone marrow or stem cell transplantation is the treatment of choice. Full engraftment results in normal platelet numbers and functions, normal immunologic status, and clearance of the dermatitis. Appropriate antibiotics, immunizations, and transfusions of platelets and plasma decrease the risk of fatal infections and hemorrhage. IVIG is useful in some patients. Topical glucocorticoid preparations may improve the dermatitis, and chronic oral acyclovir is appropriate for recurrent eczema herpeticum.

10.3.7.5 Experimental Approaches

Gene therapy has been reported as an approach to patients who are unlikely to survive allogeneic transplantation or who have undergone unsuccessful transplantation [9].

Take Home Message

- Consider WAS in patients with atopic dermatitis who have recurrent infections and screen for thrombocytopenia.

10.3.7.6 Global Variations

Internationally, treatment strategies are similar.

10.3.8 Complement Disorders

Key Features

- Deficiency or dysfunction of C1 esterase inhibitor (C1 INH) leads to hereditary angioedema (HAE), a form of angioedema without associated urticaria.
- Deficiency or dysfunction of early complement components increases susceptibility to pyogenic infections caused by encapsulated bacteria and autoimmune disorders, especially systemic lupus erythematosus (SLE).
- Deficiency of late complement components leads to a markedly increased risk of neisserial infections.

10.3.8.1 Etiology and Pathophysiology

HAE reflects an altered regulation of the complement cascade (mutations in C1 INH), leading to uncontrolled activation of the complement cascade. The reason for the increased incidence of autoimmune disorders and particularly lupus in patients with early complement deficiency is unclear, but may relate to impaired clearance of apoptotic cells of the skin and kidneys that present autoantigens; complement components are also important for handling immune complexes and maintenance of B cell tolerance. The variety of recurrent infections associated with complement deficiencies emphasizes the role of complement in bacterial clearance, including the role of the terminal complement pathway in destruction of neisserial organisms.

10.3.8.2 Clinical Characteristics and Diagnosis

HAE is characterized by repeated bouts of edema of the face, extremities, upper respiratory tract, and gastrointestinal tract without associated urticaria. Untreated patients with HAE have a morbidity approaching 50% [1]. The most commonly deficient complement component is C2, but the majority of
affected individuals are heterozygotes and show no clinical manifestations; others show milder manifestations beginning in adulthood, particularly photosensitivity, oral aphthae, lesions of subacute cutaneous lupus, and arthralgia; 75% of patients have detectable anti-Ro antibodies. Deficiency of homozygous C1q deficiency is the strongest single genetic risk factor for SLE. The bacterial organisms that cause problems in complement deficiency of classical components are encapsulated bacteria, including pneumococcus and *Hemophilus influenzae*. In contrast, with deficiency of components of the membrane attack complex (terminal complement components) or regulators of the alternative pathway, particularly properdin deficiency, infections most commonly begin in teenage years and are caused by neisserial organisms, particularly meningococcus. Progressive partial lipodystrophy involving the thoracic or cephalothoracic region has been described with hereditary deficiency of C3; affected individuals may also show associated membranoproliferative glomerulonephritis, insulin resistance, and an increased incidence of autoimmune diseases. In complement deficiencies other than HAE, total hemolytic complement (CH50) is markedly decreased (e.g., in C9 deficiency) or undetectable (most complement deficiencies). The alternative pathway lytic test (AP50) is less sensitive than the CH50, but may be useful to screen for deficiency of the alternative pathway components. Low levels of C1 INH suggest HAE, but when C1 INH level is normal, functional C1 INH can be detected by radial immunodiffusion assays that measure C1r; C4 levels can screen for HAE, since virtually all untreated patients with HAE have decreased serum levels (<30% of normal).

### 10.3.8.3 Current Established Therapies

Long-term prophylaxis with anabolic androgens or antifibrinolytics (aminocaproic acid or tranexamic acid) is used for patients with significant swelling of the gastrointestinal tract, head or neck that occurs more frequently than once a year, frequent peripheral or genital area swelling, requirement for fresh frozen plasma more than once a year, or in a patient with a history of airway compromise [41]. Immunization of the patient with late complement component deficiency and household contacts for pneumococci, *H influenzae*, and *N meningitides* can decrease the risk of those disorders.

### 10.3.8.4 Experimental Approaches

Intravenous injection of purified C1 INH is the most effective modality of treatment for acute attacks; however, neither purified plasma-derived nor recombinant C1 INH is approved for use in the United States. Agents such as kallikrein and B2-bradykinin inhibitors may represent additional options for therapy [42].

### 10.3.8.5 Complications to Avoid

Airway obstruction is a medical emergency in patients with HAE, and intubation may be required to maintain patency. Attacks are often precipitated by minor trauma or emotional stress, and dental surgery is an important trigger for laryngeal attacks [3]. Androgens are contraindicated in children because of growth retardation, except for short courses before surgery or dental work.

### Take Home Message

- Consider deficiency of early complement components in patients with autoimmune disorders, particularly lupus; late complement component deficiencies in older children and young adults with recurrent gonococcal or meningococcal infections; and HAE in association with recurrent angioedema without typical urticaria.

### 10.3.8.6 Global Variations

Internationally, treatment strategies are similar.
10.3.9 Chronic Granulomatous Disease (CGD)

Key Features

- Inability to kill intracellular organisms through generation of oxidative metabolites
- X-linked recessive or autosomal recessive inheritance
- Recurrent pneumonias and cutaneous infections, lymphadenopathy, and hepatosplenomegaly
- Patients develop granulomas as a compensatory effort to confine organisms

10.3.9.1 Etiology and Pathophysiology

CGD is caused by defects in reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, the enzyme complex responsible for the generation of superoxide [28]. Oxidative molecules act as intracellular signaling molecules, activating the release of primary granule proteins, neutrophil elastase and cathepsin G inside the phagocytic vacuole that are needed to kill microbes [26]. In X-linked kindreds the CYBB gene encoding the gp91phox (phagocyte oxidase) subunit of cytochrome b558 is mutated. Patients with autosomal recessive CGD are deficient in NADPH oxidase cytosolic factors (p47phox or p67phox); occasionally the p22phox (γ subunit of cytochrome b558) which contains a docking site for p47phox is deficient.

10.3.9.2 Clinical Characteristics and Diagnosis

Pyodermas with associated regional lymphadenopathy and dermatitis, especially around nares and ears, usually occur during infancy and rarely in neonates. Staphylococcal abscesses are found in 40% of patients, particularly in the perianal area. Purulent inflammatory reactions may develop at sites of lymph node drainage or minor cutaneous trauma, and heal slowly with scarring. Patients with CGD often develop chronic inflammatory granulomas, most commonly of the lungs and liver. Female carriers for X-linked CGD do not have the increased risk of infections but may have cutaneous lesions of discoid or SLE, aphthous stomatitis, photosensitivity, and/or Raynaud phenomenon.

10.3.9.3 Current Established Therapies

Infection should be treated empirically with broad-spectrum parenteral antibiotics that cover S. aureus as well as gram-negative organisms. Surgical interventions (drainage, debridement) may be required for deeper infections. Itraconazole is an effective agent for prophylaxis of fungal infections [12]. Patients with X-linked CGD, p22phox CGD, and p67phox CGD tend to have a more severe clinical course compared to patients with p47phox CGD.

10.3.9.4 Experimental Approaches

Interferon-γ prophylaxis may reduce the risk of infection and may be relatively well tolerated over a prolonged period of time [18]. Corticosteroid therapy may also play an adjunctive role in refractory infections [40]. Leukocyte transfusions have been used for rapidly progressive, life-threatening infections. Stem cell-gene therapy has been used successfully [14]. Allogeneic bone marrow transplantation may provide a definitive cure but it carries a significant risk [30].

10.3.9.5 Complications to Avoid

Although transplantation has been performed, its use is limited by procedure-related toxicities, GVHD, and death; it should only be considered for those with severe, life threatening infections despite appropriate medical care.
10.3.9.6 **Global Variations**

Internationally, treatment strategies are similar.

10.3.10 **Leukocyte Adhesion Deficiency (LAD)**

10.3.10.1 **Etiology and Pathophysiology**

LAD affects the ability of neutrophils to adhere to endothelium, tissue matrix, and microbes. A mutation in the gene encoding CD18 leads to absent or deficient surface glycoproteins in LAD 1. As a result, neutrophil and monocyte chemotaxis and phagocytosis are impaired. Rarer variants of LAD include LAD type 2 (LAD-2) and type 3 (LAD-3).

10.3.10.2 **Clinical Characteristics and Diagnosis**

Patients have frequent infections of the skin and respiratory and gastrointestinal tract often caused by *S. aureus* or gram-negative enteric bacteria. Skin infections are often precipitated by puncture wounds or skin surface trauma and begin as small erythematous or necrotic abscesses, progressing to large ulcerative lesions that resemble pyoderma gangrenosum. Poor wound healing leads to paper-thin or dysplastic cutaneous scars. Cellulitis of the face and perirectal area is common. Gingivitis with periodontitis results in loss of teeth.

10.3.10.3 **Current Established Therapies**

Antimicrobial therapy is the mainstay of treatment. Skin ulcers often require grafting. Bone marrow transplantation restores leukocyte function and is recommended in patients with the severe phenotype.

10.3.10.4 **Experimental Approaches**

Preimplantation genetic diagnosis of LAD-I has led to the birth of a normal child. A canine model of LAD-I has facilitated development of new nonmyeloablative hematopoietic stem cell transplant and gene therapy approaches to LAD [17]. Successful transplant of cord blood from HLA-identical siblings has been reported. Gene therapy introducing the normal CD18 subunit gene into affected hematopoietic stem cells has successfully restored CD18 expression. The ex-vivo transfer of CD18 into affected cells, followed by infusion of the transduced cells may represent another therapeutic approach [2].

10.3.10.5 **Global Variations**

Internationally, treatment strategies are similar.

---

**Take Home Message**

- Consider CGD in patients with recurrent bacterial infection without cytopenia or other clear cause.

**Key Features**

- Gingivitis and periodontitis
- Necrotic ulcerations resembling pyoderma gangrenosum
- Poor wound healing; delayed separation of the umbilical stump
- Life-threatening bacterial and fungal infections

**Take Home Message**

- Check for gingival inflammation in young patients with recurrent infections who present with cutaneous ulcers.
10.3.11 Hyperimmunoglobulinemia E Syndrome (HIES)

**Key Features**
- An autosomal dominant disorder with variable expressivity, characterized by extremely high IgE levels
- Recurrent infections of the skin (particularly “cold abscesses”) and sinopulmonary tract with *S. aureus* and, especially during infancy, *C. albicans*
- Papulopustular facial eruption during infancy
- Most have atopic-like dermatitis
- Coarse facial features, osteopenia with fractures, scoliosis, and dental abnormalities

10.3.11.1 Etiology and Pathophysiology

The gene for HIES has been mapped to the proximal arm of chromosome 4q, although the underlying cause of hyper-IgE syndrome is still unknown [8].

10.3.11.2 Clinical Characteristics and Diagnosis

Neonatal or infantile rash of hyper-IgE syndrome is often a papulopustular eruption with prominent crusting distributed on the scalp, face, neck, axillae, and diaper area. In other infants, early candidal infections of the skin, mucosae, and nails and/or infantile atopic dermatitis are alternative presentations. Superinfection of the dermatitis with *S. aureus* is very common [11] and patients show high levels of antistaphylococcal IgE antibodies. Staphylococcal skin infections include characteristic “cold” abscesses.

10.3.11.3 Current Established Therapies

Antistaphylococcal antibiotics are effective for most cutaneous infections in patients with HIES, and oral triazole antifungals treat the mucocutaneous candidiasis. Prophylactic use of antistaphylococcal antibiotics markedly reduces the incidence of skin abscesses and pneumonia. Cutaneous and pulmonary abscesses often require incision and drainage and may require partial lung resections. IVIG therapy has been used successfully.

10.3.11.4 Experimental Approaches

Therapy is directed at prevention and management of infections by using sustained systemic antibiotics and antifungals along with topical therapy for eczema and drainage of abscesses. Interferon, immunoglobulin supplementation, or low-dose cyclosporine have been reported to benefit selected patients, but they are not generally indicated [13, 39]. Bone marrow transplant has been attempted with limited success. A variety of agents such as levamisole, ascorbic acid, and lithium have been anecdotally reported to reduce the likelihood of recurrent infection [19].

10.3.11.5 Complications to Avoid

Normal IgE levels in infants and young children are much lower than in adults; levels 10 times above the 95th percentile for age should raise suspicion.

**Take Home Message**

- Keep HIES in mind in patients with atopic dermatitis who have early candidal and staphylococcal infections, especially with staphylococcal abscesses.

10.3.11.6 Global Variations

Cimetidine has been used for its stimulatory effects on neutrophil chemotaxis in those who respond poorly to antibiotics [29].
10.3.12 Silvery Hair Syndromes

**Key Features**

- Autosomal recessive disorders of melanosome (and other organelle) transfer lead to clumping of melanosomes
- Silvery hair, mild diffuse pigmentary dilution (often with an admixture of hyper- and hypopigmentation in sun-exposed sites)
- Recurrent pyogenic infections and a mild bleeding diathesis
- An “accelerated phase” with pancytopenia and organomegaly due to lymphohistiocytic infiltration (fatal without hematopoietic stem cell transplantation, HCT)

10.3.12.1 Etiology and Pathophysiology

Chediak-Higashi syndrome (CHS) is caused by mutations in the LYST (lysosomal transport) gene, which encodes a protein required for the final steps of vesicle trafficking and secretion [34]. Mutations in one of two genes may underlie Griscelli syndrome (GS) in humans. GS1 is caused by a mutation in the MYO5A gene that encodes myosin 5a, a motor protein responsible for intracellular organelle transport. GS2 is caused by a mutation in the RAB27A gene which encodes Rab27a, a GTPase protein involved in the function of the intracellular-regulated secretory pathway.

10.3.12.2 Clinical Characteristics and Diagnosis

The pigmentary dilution of GS is often limited to silvery hair, while in CHS the skin characteristically has a dull sheen and can show acral areas of intense hyperpigmentation. Infections can begin as early as the neonatal period, and most commonly involve the skin, lungs, and respiratory tract. Patients with immune dysfunction and GS are likely to have GS2, and develop hemophagocytic syndrome (“accelerated phase”) with visceral infiltration by activated lymphocytes and macrophages, associated with infections and a bleeding diathesis. Hepatosplenomegaly, lymphadenopathy, pancytopenia, jaundice, fever, a leukemia-like gingivitis, and pseudomembranous sloughing of the buccal mucosa are common features of the accelerated phase; infiltration of the CNS may lead to neurologic dysfunction in GS2. Individuals with GS1 primarily have neurological disease with hypotonia and early developmental delay, but not hemophagocytic syndrome. Neurologic deterioration in CHS is progressive.

The finding of large cytoplasmic granules in blood leukocytes is highly diagnostic for CHS. Pigment granule clumping is seen in both CHS and GS, but the granules are smaller and evenly distributed in CHS, and larger and irregular in GS.

10.3.12.3 Current Established Therapies

The treatment of choice for patients with CH and GS is early transplantation, which corrects the immunologic status, but neither affects the pigment abnormality nor inhibits the development of progressive neurologic dysfunction in Chediak-Higashi.

10.3.12.4 Experimental Approaches

Although numbers are limited, HCT appears to be an effective therapy for correcting and preventing hematologic and immunologic complications of CHS, and an unrelated donor may be a suitable alternative for patients without an HLA-matched sibling. Early referral and transplantation in remission after the accelerated phase of disease may improve disease-free survival [10]. Acyclovir, high-dose IVIG, vincristine, cyclosporine, and prednisone have also been used to control the accelerated phase of CHS, with limited success. Interferon has been reported to partially restore NK cell function.
10.3.12.5 Global Variations

Internationally, treatment strategies are similar.

References

10.4.1 What is DNA repair? [1, 2]

DNA repair is a very important function for all living organisms exposed to sunlight. Efficient removal of UV-induced DNA lesions is vital for survival. The nucleotide excision repair (NER) system is mainly responsible for correcting UV-induced damage in DNA; these are predominantly cyclobutane pyrimidine dimers (CPD) and 6-4 pyrimidine-pyrimidone photoproducts (6-4PP) (Fig. 10.4.1). More than 25 proteins are involved in this system, several of which are also related to the transcription of mRNA. Photoproducts are not randomly repaired by NER throughout the genome. Lesions in DNA that are actively transcribed by RNA polymerase II are repaired more rapidly (transcription-coupled repair (or TCR)) than those in the global genome or in the non-transcribed strand of active genes (global genome repair (or GGR)). The first recognition of DNA damage involves CSA and CSB proteins in TCR and DNA damage binding protein (DDB) plus XPC-hHR23B-centrin 2 in GGR. XPA, transcription factor II H (TFIIH), and replication protein A (RPA) are involved both in TCR and GGR. TFIIH, a basal transcription factor, contains two kinds of DNA helicase activity; XPB and XPD with opposite direction (3'->5', 5'->3', respectively), which play an important role in DNA unwinding of the double strand DNA. After the recognition of the DNA damage, two endonucleases XPF-ERCC1 and XPG, make incisions 5'–3' to the lesion releasing a 25–27 nucleotide DNA fragment containing the photoproduct. The resulting gap can be filled by a process involving DNA polymerases, ε/δ, proliferating cell nuclear antigen (PCNA), and replication factor C (RFC), followed by sealing with DNA ligase I. This NER pathway removes the lesion containing the damaged DNA and restores the normal DNA sequence using the opposite strand as a template.
10.4.2 Clinical Characteristics and Diagnosis of Disorders Related to DNA Repair Deficiency

10.4.2.1 XP

XP is a rare autosomal recessively transmitted cancer-prone genodermatosis involving impaired repair of UV-induced DNA damage. XP patients have severe sensitivity to sunlight and a high incidence (more than 1,000-fold increase compared to the normal population) of skin cancers: basal cell cancers (BCC), squamous cell cancers, and melanoma [2, 3]. There is a smaller increase in internal neoplasms including cancer of the central nervous system. About 20–30% of XP patients have neurological disease such as mental retardation, sensorineural...
 Disorders of DNA repair

10.4 Disorders of DNA repair

deafness, and abnormal motor function (spasticity) in association with a primary progressive neuronal degeneration [4]. MRI in XP may show progressive cerebral atrophy with enlargement of the ventricles. While multiple infections are not common in XP, there are reports of impaired immune response such as impaired production of interferon-gamma, interferon-alpha, IL1-beta, and IL-6 [5, 6]. The molecular basis of XP neurological abnormalities and impaired immune function still remain to be elucidated. Cultured cells derived from most XP patients show hypersensitivity to killing by UV irradiation, reduced DNA repair capacity, and high frequency of UV-induced mutations. There are seven genetically different complementation groups (defective genes), XPA through XPG, with defective NER and one excision repair proficient form with deficient DNA polymerase eta (XP variant). XP group A, a severe form of XP with marked neurological degeneration, is more common in Japan (about 55% of Japanese XPA patients) than in US and Europe where 40% of XP cases are XP group C [7, 8]. Previously the diagnosis of XP was made by DNA repair tests such as the measurement of post-UV unscheduled DNA synthesis (UDS), UV survival by colony formation or complementation assay by somatic cell fusion technique. Now the assignment of complementation group of XP has mainly been made by plasmid host cell reactivation (HCR) assay and gene analysis. The recent identification and characterization of the genes responsible for XP (group A through G and variant) permit the use of molecular biological techniques for the sensitive diagnosis of XP. These techniques include polymerase chain reaction (PCR) – RFLP analysis, DNA sequencing, and plasmid HCR assay with cloned XP genes. Plasmid HCR assay is an easier, more rapid and more sensitive laboratory assay for the diagnosis of XP than the classical method; cell fusion assay [7]. HCR utilizes an ultraviolet (UV)-treated plasmid containing the sequence of a reporter gene such as luciferase in addition to cloned expression vector of each XP group. The disadvantage of the assay is that XP group E and XP variant cannot be determined. Most of Japanese XP patients are homozygous or heterozygous for a founder mutation: a G to C transversion at the 3’ splice acceptor site of intron 3 in the XPA gene. This mutation is conveniently identified with a restriction enzyme, AlwNI. PCR-RFLP method permits rapid diagnosis, carrier detection, and prenatal diagnosis of XP, especially in Japanese XPA families [7].

10.4.2.2 CS

CS is a rare autosomal recessive disease with features of sun sensitivity, short stature, pigmentary retinal degeneration, hearing loss, and progressive neurological degeneration [9]. MRI in CS may show absence of myelin in the cerebrum. CT scan in CS may show calcification of the basal ganglia. Unlike XP, CS is not associated with an increased frequency of skin cancers. CS patients have a deficiency of transcription-coupled NER of UV-induced DNA damage. Cells from CS patients are hypersensitive to killing by UV, have decreased post-UV RNA synthesis, and normal level of post-UV UDS [7]. The genes for CS, CSA, and CSB have been cloned. To define the complementation group, HCR is useful as in cases of XP. Alterations of XPB, XPD and XPG gene can sometimes cause CS phenotype in addition to XP lesions such as freckles and skin neoplasms and these cases are diagnosed to be XP/CS complex [4, 10, 11].

10.4.2.3 TTD

TTD is an autosomal recessive disorder with features of sulfur-deficient brittle hair (with characteristic “tiger tail” banding with polarized microscopy), ichthyosis, short stature, nail dystrophy, cataracts, multiple infections, and neurological abnormalities [12]. MRI in TTD may show decreased or absent myelin in the cerebrum. About 50% of TTD patients have sun sensitivity. There is no increase in skin cancer [13]. Cells from photosensitive TTD patients have defects in XPD, XPB, and TTDA genes, all of which are components of TFIIH [14]. Cells from photosensitive TTD cases are hypersensitive to UV and have reduced level of UDS. Cells from some TTD patients without sun sensitivity have normal UV survival and normal UDS and a defect in the TTDN1 gene. To determine the genetic group of photosensitive form of TTD, HCR assay is useful as in XP and CS.

10.4.3 Management of Patients with XP, CS or TTD and Therapeutic Outline

XP patients may present with many cutaneous malignancies and continue to form skin cancer at a high rate. As there is no cure for genetic disorders, life-long
protection of XP patients from UV radiation and early recognition and prompt treatment of skin cancers are essential. CS and TTD patients do not have an increased risk of skin cancer.

Clinical management of XP consists of early diagnosis followed by a rigorous program of sun protection including avoidance of unnecessary UV exposures, wearing UV blocking clothing, (Fig. 10.4.2) and use of sun blocks on the skin. Sun protection with sunscreen should be done as completely as possible to prevent photodamage of the skin. Exposure to cigarette smoke should be avoided since it contains carcinogens that damage DNA in a manner similar to UV.

A series of baseline skin photographs is often helpful in early detection of skin cancers. Suspicious lesions should be biopsied readily. Premalignant lesions such as actinic keratoses can be treated by freezing with liquid nitrogen or by 5-fluorouracil ointment. Imiquimod, an immune response modifier through the induction of IFN-alpha, INF-gamma, TNF-alpha, IL-6, and IL-12 appears to be safe for BCC in XP patients. [15]. Clearing of multiple melanoma in situ lesions by local injection of interferon alpha has been reported in one patient [16].

Surgical resection of skin tumors utilizing standard methods, including Moh’s microsurgery, can be used. This approach should attempt to preserve surrounding undamaged tissue for possible further procedures. Clear margins of pigmented lesions may be difficult to achieve because of the widespread pigmentation of surrounding skin. Larger areas have been treated with therapeutic dermatome shaving or dermabrasion to remove the damaged superficial epidermal layers. This procedure permits repopulation by relatively UV-shielded cells from the follicles and glands. Standard doses of radiotherapy have been used for treatment of unresectable cancers of the skin or central nervous system. Cells from XP patients are not hypersensitive to killing by X-rays. On the other hand, there is a recent report of worsening of an eye tumor following treatment with photodynamic therapy (PDT); so this treatment cannot be recommended [17].

Oral isotretinoin (13-cis retinoic acid), a vitamin A derivative, has been shown to prevent the appearance of new skin neoplasms in XP patients; however, this treatment has many side effects [18]. The topical use of T4 endonuclease V, a prokaryotic DNA repair enzyme which initiates repair of UV-induced CPD in DNA may be a useful tool to prevent new appearance of actinic keratosis or other skin tumors in XP patients [19]. This agent has not yet been approved by the US Food and Drug Administration.

XP patients often have problems with their eyes such as conjunctivitis, corneal clouding, cataract, and ocular neoplasms at a much younger age than in the general population. Dry eyes are common and should be treated with lubrication. To avoid these ocular symptoms, patients should use sunglasses which block UV light. CS patients often develop a retinal degeneration. Ophthalmologic involvement in TTD commonly includes bilateral cataracts (which may be congenital and require early surgical treatment), nystagmus, and errors of refraction.

Some XP patients and most CS patients have neurological symptoms which progress gradually. Care (rehabilitation) for neurological abnormalities including use of hearing aids for patients with hearing loss is essential. Progressive neurological symptoms frequently seen in patients with defects in the XPA, XPB, XPD or XPG genes may be difficult to manage. Patients with XP neurodegeneration may have problems with walking, talking, and caring for themselves. They may experience progressive loss of intellectual functioning. Rehabilitation therapy may be beneficial. Patients should have periodic evaluations by experts in ophthalmology, orthopedics, neurology, and dentistry as well as by dermatologists.

TTD patients may have developmental delay and intellectual impairment. They may benefit from neurologic and developmental assessment. Some TTD patients have recurrent infections which have been managed with prophylactic antibiotics or intravenous immunoglobulin G (IVIG). TTD patients with skeletal abnormalities may benefit from rehabilitation medicine evaluation and support.

**10.4.4 Experimental Approaches**

Recently a gene therapy of XP cells or XP mice has been reported [20]. When DNA containing an XPA complementing gene was applied to XPA mouse skin using liposomes, the level of UDS after UV exposure
was increased and the DNA damage was repaired almost normally (personal communication). Functional lentiviral, adenovirus or retrovirus vectors have been reported to restore DNA repair ability of XP cells or UV-irradiated mice [21–25]. Topical application of epigallocatechin, the major polyphenol of green tea, has been reported to prevent photocarcinogenesis in mice through IL12-dependent DNA repair mechanism [26]. These research methods offer hope for the future.

**Take Home Messages**

- Disorders of post-UV DNA repair deficiency, such as XP, CS or TTD are very rare photosensitive genodermatoses. When physicians see cases with sun sensitivity in clinic, they should consider these rare diseases in the differential diagnosis. Early diagnosis and protection from sun exposure can improve the patients’ prognosis.
Patient support groups have been established in several countries that provide information and resources for patients and their family; several have established summer camps with a UV protected environment. The Xeroderma Pigmentosum Society is an educational, advocacy, and support organization in New York: http://www.xps.org. The XP Family Support Group is located in California http://www.xpfamilysupport.org/ The XP Support Group in the UK has a website: http://xpsupport-group.org.uk/ A group in Germany has a website: http://www.xerodermapigmentosum.de/ A Japanese group of XP families has a website: http://www.xp-japan.net/ Enfants de la lune (Children of the moon) in France: http://www.orpha.net/legacy/AXP/ A web site listing disease-causing mutations in XP and CS genes has been established: http://xpmutations.org/.

The booklet “Understanding Xeroderma Pigmentosum,” prepared by the National Institutes of Health, is available on the Internet at http://www.cc.nih.gov/ncic/patient_education/pepubs/xp5_18.pdf This booklet provides information about XP for patients, their families, educators, students, health professionals, media inquiries, and others interested in learning more about XP.

There is an educational, advocacy, and support organization for helping patients with CS and their families: The Share and Care Cockayne Syndrome Network in Texas: http://www.cockayne-syndrome.org The Japanese Cockayne Syndrome Network.

10.4.5 Global Variations

Oral Isotretinoin has been shown to be effective in preventing new skin cancers in XP patients in a controlled study [18]. Topical Imiquimod can be used in Europe and the US but this agent has not been shown to be beneficial in a controlled study. Topical T4 endonuclease V was reported to be beneficial in a small study with XP patients [19] but has not yet been approved for use by the US Food and Drug Administration. XP patients in Japan tend to have mutations that lead to progressive neurological degeneration while those in Europe and the US tend to have predominantly skin and anterior eye involvement.

References


This chapter focuses on the two most common non-melanoma skin cancers (NMSCs), basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs). NMSC is the most common form of human malignancy, with about 75–80% being BCCs and about 20–25% being SCCs. It is estimated that one in five Americans will develop a skin cancer during their lifetime, with about 97% being NMSC [89]. Most epidemiological studies show that NMSC rates are increasing worldwide, possibly as a consequence of increased cumulative UV-exposure, increasing lifespan of the population, and increasing awareness and detection of NMSCs. This increase in NMSC incidence is associated with an increasing economic burden on the health care system [7]. The highest incidence rates have been reported in populations with light skin types living in regions of high UV exposures, such as in Australia, where more than 1% of the population develops NMSCs per year [22]. Cumulative risks to age 70 years of having at least one NMSC were 70% for men and 58% for women in a survey conducted in Australia [103]. The incidence of NMSC correlates directly with annual exposure to solar UV radiation.

Mortality rates for SCCs are age-dependent. While melanomas have the highest mortality rate among skin cancers in whites under the age of 50, SCCs have the highest mortality rates among whites older than 85 years [124]. BCCs generally grow locally and do not metastasize and are still a cause of significant morbidity if left untreated [117]. These epidemiological data highlight the importance of utilizing photoprotective strategies early in life including protective clothing, the use of sunscreens and regular skin cancer screening to prevent and detect NMSCs as early as possible.
11.1.1 BCC

11.1.1.1 Etiology and Pathophysiology

The genetic basis for developing BCCs was first substantiated with the identification of the causative gene mutations in the autosomal dominant nevoid BCC syndrome, also known as Gorlin syndrome [32, 41]. This syndrome is characterized by multiple BCCs, palmar and plantar pits, odontogenic keratocysts of the jaw, skeletal abnormalities, and calcification of the falx cerebri. In the original publications that describe the identification of mutations in the human homologue of the Drosophila patched (PTCH) gene of the Sonic hedgehog (Shh) signaling pathway in hereditary nevoid BCC syndrome, hemizygous mutations in PTCH were also found in sporadic BCCs that showed allelic loss of the PTCH gene. Such inactivating mutations in the remaining PTCH allele in BCCs, leading to a loss of heterozygosity, are consistent with a tumor suppressor function of PTCH. Subsequently, mutations in PTCH were detected in almost one third of sporadic BCCs [27]. Germline mutations in PTCH in patients with nevoid BCC syndrome demonstrate the importance of the Shh signaling pathway not only for tumorigenesis, but also for its role during development, which is reflected in the developmental abnormalities seen in these patients. In fact, patched and hedgehog are highly conserved genes that were initially identified as segment polarity genes in the fruitfly Drosophila melanogaster during embryonic development.

It was subsequently shown that Patched forms a complex with its co-receptor Smoothened, a transmembrane G-protein-coupled receptor, thereby inactivating its downstream signaling (Fig. 11.1.1). When Smoothened is not part of a complex with Patched, it is constitutively active. Sonic hedgehog was shown to bind to Patched, resulting in dissociation from Smoothened, and thereby activating downstream signaling [109], mediated by Gli transcription factors. Inactivating PTCH mutations result in constitutive activation of Smoothened and augmented signaling via Gli proteins, leading to transcription of target genes that drive cell proliferation. Activating mutations in Smoothened have a similar effect and have been identified in sporadic BCCs as well [128].

Gli is a transcription factor that regulates the expression of several genes, including its own and the expression of Patched, thereby having a negative feedback effect on Shh-Patched signaling. Upregulation of Gli has been shown to increase cellular proliferation. A central role for Gli proteins in BCC formation was established in a mouse model that overexpresses Gli2 in the epidermis [38]. Inducible overexpression of Gli2 in the epidermis of mice resulted in the growth of BCCs that arose from hair follicle epithelium. Inactivation of the Gli2 transgene led to regression of BCCs due to tumor cell apoptosis, demonstrating that BCC growth is dependent on continuously activated Shh-signaling. Furthermore, it was demonstrated that regressing BCC cells in this mouse model were able to give rise to normal-appearing epithelial cell lineages in hair morphogenesis experiments, raising the possibility that BCCs represent an aberrant form of hair follicle organogenesis [38].

An important role of the Shh-signaling pathway for the development of several different tumors has been suggested by the identification of PTCH mutations in these tumors, some of which are also observed more frequently in patients with the hereditary nevoid BCC syndrome, such as medulloblastomas. In addition, inactivating mutations in PTCH occur in sporadic trichoepitheliomas and to a lesser extent in other extracutaneous...
tumors [127]. Mice heterozygous for the Patched gene also develop rhabdomyosarcomas with higher frequency, and manifest a high incidence of radiation-induced teratogenesis [33]. Similarly, patients with nevoid BCC syndrome show increased sensitivity to ionizing radiation. The increased frequency of BCCs in patients with nevoid BCC syndrome particularly in sun-exposed sites and with increasing age, also suggests that solar UV radiation contributes to the development of BCCs in these patients. Sporadic BCCs on the trunk have been associated with excessive intermittent sun exposure, particularly with the number of severe sunburns and solar lentigines on the trunk [70]. Individuals with fair skin (Fitzpatrick Skin Types I and II) are at enhanced risk for the development of BCCs, as confirmed in genome-wide association studies that linked variants in genes affecting pigmentation to an increased risk of developing BCCs [31].

Notably, inhibition of Smoothened signaling in Patched heterozygous mice with the Smoothened antagonist cyclopamine reduced UVB-induced BCCs in these mice, associated with increased Fas expression and an increased rate of apoptosis [2]. A high rate of UV-induced mutations in Smoothened was identified in BCCs in UV-hypersensitive patients with xeroderma pigmentosum, while no mutations in Smoothened were identified in SCCs from these patients. These findings demonstrate a strong association between activated Smoothened and the development of BCCs.

In addition to mutations in genes of the Shh-Patched signaling pathway in BCCs, mutations in the p53 tumor suppressor gene have been identified in about 40–60% of sporadic BCCs, with the majority of the mutations being presumably UV-induced transition mutations at dipyrimidine sites [87, 133]. Point mutations in the p53 gene are frequently accompanied by a second point mutation on the corresponding allele [133].

The identification of mutations in genes that promote proliferation and clonal expansion of cells is consistent with a unicellular origin of BCCs, which has been demonstrated in clonality assays for a majority of BCCs [95, 121]. Notably, p53 gene mutation analyses have suggested that there is a development of subclones within different components of a BCC with acquisition of additional p53 gene mutations [83].

BCCs, in contrast to other types of NMSCs, grow locally resulting in tissue destruction, but very rarely metastasize. Even continuous exposure to mutagenic UV-radiation is unlikely to increase the risk of metastasis of BCCs. It has been proposed that the reason why BCCs usually do not metastasize may lie in a growth dependence of BCC cells on their adjacent stroma. Therefore, epithelial-mesenchymal interactions may limit the aggressive growth of BCCs. In fact, it has been shown that BCC cells express growth factors for which their receptors are upregulated in adjacent stromal cells. Expression analyses of stromal fibroblasts adjacent to BCCs identified a specific expression profile of these fibroblasts when compared to those isolated from SCCs, which could explain the stroma-dependency and characteristic growth behavior of BCCs [67]. Moreover, variations in epithelial-stromal interactions may explain the distinct morphological subtypes of BCCs and their distinct growth characteristics. It has been demonstrated that morpheaform BCCs, characterized by a more aggressive infiltrative growth pattern than that seen in nodular BCCs, express significantly higher levels of $\alpha_v\beta_6$-integrins [65]. $\alpha_v\beta_6$-integrin-dependent activation of TGF-β resulted in a transdifferentiation of human fibroblasts into myofibroblasts in vitro, a finding that is consistent with the increased presence of myofibroblasts in morpheaform BCCs when compared to nodular BCCs. These myofibroblasts expressed growth factors (such as hepatocyte growth factor) that promoted tumor cell invasion through a paracrine effect. The data support the concept of a stroma-dependency of BCCs and that the various growth patterns observed in BCC subtypes are a likely consequence of distinct epithelial-stromal interactions.

Global gene expression analyses of stromal cell cultures derived from human BCCs, revealed an important role of bone morphogenetic protein (BMP) signaling pathways in sustaining BCC growth. The BMP antagonist Gremlin-1 was overexpressed in the stroma of BCCs, which was shown to stimulate proliferation of BCC cells in culture [101]. Thus, stromal cells provide a favorable microenvironment for BCC cell proliferation and infiltrative growth, while their absence limits the ability of BCC cells to grow and metastasize.

### 11.1.2 Clinical Characteristics and Diagnosis

BCCs are the most common type of NMSC, being about three to four times more common than SCCs in the United States. Incidence rates are influenced by
BCCs may be pigmented (Fig. 11.1.2d). It is important to distinguish pigmented BCCs from atypical melanocytic lesions and malignant melanoma.

Superficial BCCs often appear as banal erythematous macules, papules or plaques, commonly located on the trunk and extremities. Superficial BCCs may resemble benign entities, such as nummular dermatitis, as well as actinic keratoses or Bowen’s disease. Superficial BCCs have a higher recurrence rate compared to nodular BCCs, likely due to subclinical lateral spread.

Morpheaform BCCs have a sclerotic appearance and are often indurated (Fig. 11.1.2c). Importantly, this form of BCC may be significantly larger than it appears clinically, explaining the higher recurrence rates after surgical excision of this variant of BCC.

A cystic BCC may appear clear or bluish, and resembles nodular BCCs. A less common variant of BCC is the so-called basosquamous carcinoma (Fig. 11.1.2e). Histologically, basaloid cells are seen as in BCCs, but eosinophilic squamoid changes as seen in SCCs occur as well. Consistent with its mixed histological features, its clinical course can be more aggressive, mimicking SCCs. Although this form of BCC is rare (1%), the exceptionally rare occurrence of BCC metastases is more commonly found with this variant (about 10% of metastases).

Fibroepithelioma of Pinkus has been traditionally described as a variant of a BCC, often presenting as a pink papule on the lower back that can be pedunculated. These lesions have a benign histological appearance with follicular germinative differentiation and should be considered as a variant of a benign trichoepithelioma, rather than a BCC [8].

Histologically, BCCs are characterized by atypical cells with large nuclei and scant cytoplasm that form tumor islands (Fig. 11.1.3). The histologic and immunohistochemical features of basaloid cells from BCCs are strikingly similar with those of cells from the suprabulbar region of the outer root sheath and cells from the bulge region of vellus hair follicles [51]. These findings support the hypothesis that BCCs are derived from follicular epithelium. Positive immunostaining for cytokeratin 15, which labels the hair follicle bulge region, occurs in trichoepitheliomas and in a subset of BCCs, further supporting the hypothesis that BCCs may be derived from epithelial stem cells in the hair follicle bulge [40].

Basaloid cells in BCCs are surrounded by a dense mucin-rich fibromyxoid stroma, which shows a characteristic retraction histologically that manifests as microscopically visible clefts between the stroma and the

latitude and ethnicity, since UV-exposure and skin pigmentation influence the development of BCCs. Epidemiological studies indicate that the incidence of BCCs is about 2% in Australian men [22], with a trend of a world-wide increase in BCC incidence rates. In contrast, BCCs are rare in darkly pigmented races. Intermittent intense recreational sun exposure in childhood and adolescence augment the risk of BCCs, whereas cumulative sun exposure does not. Notably, BCCs are less common in Southern European populations.

Once a BCC develops the patient has a significantly higher risk for developing additional lesions [64]. Other factors that increase risk include exposure to ionizing radiation, arsenic, and PUVA therapy [45]. BCCs are also increased in solid organ transplant recipients receiving immunosuppressive therapy [39]. The normal ratio of BCCs to SCCs is approximately 4:1 before renal transplantation and reverses (1:2) after transplantation. NMSC rates increased with the duration of immunosuppression [85]. The incidence rate of NMSCs was over 47% in a study in kidney transplant recipients with more than 20 years of immunosuppression [17]. BCCs occur most commonly on the sun-exposed areas of the head and neck, followed by the trunk. Interestingly, for unknown reasons, BCCs rarely occur on the sun-exposed dorsal hands. BCCs are rare in the genital area, but scrotal BCCs have a relatively high frequency of metastasis [69].

There are different morphologic variants of BCCs with characteristic clinical and histological features, including nodular, superficial, morpheaform, micronodular, cystic, keratotic (Fig. 11.1.2b) and basosquamous BCCs. Histologic examination of BCCs in one study revealed that 21% of BCCs were of the nodular type, 17% were of the superficial type, 15% of the micronodular type, 7% of the infiltrative type, and 1% of the morpheaform type, while a mixed pattern was observed in 38.5% [94]. Consistent with the well-circumscribed histologic appearance, nodular and superficial BCCs have the lowest recurrence rate after simple surgical excision as compared to the morpheaform, micronodular or mixed types.

Clinically, nodular BCCs usually present as translucent pearly papules or nodules with prominent arborizing telangiectasias (Fig. 11.1.2a). As the lesion progresses a central ulceration may form, which may lead to significant tissue destruction. Some nodular BCCs may be pigmented (Fig. 11.1.2d). It is important
11.1 Nonmelanoma Skin Cancer

These clefts are probably due to fixation-induced mucin shrinkage. Nodular BCCs often show prominent peripheral palisading (Fig. 11.1.3c and d). In addition, central ulceration within tumor islands may be seen (Fig. 11.1.3c). The tumor islands are much smaller in micronodular BCCs and often lack a retraction artifact (Fig. 11.1.3f). Micronodular BCCs can also extend into the subcutis and have a much more diffuse infiltration pattern, explaining higher recurrence rates after surgical excision.

In contrast, superficial BCCs form small interconnected basaloid tumor islands that bud off the epidermis and are separated by skip areas (Fig. 11.1.3e). They usually do not infiltrate beyond the papillary dermis. So-called keratotic BCCs or BCCs with follicular differentiation contain small keratinized cysts and need to be distinguished histologically from trichoepitheliomas. Morpheaform BCCs typically show strands of basaloid cells that extend into the dermis along dense collagen fibers (Fig. 11.1.3a and b). Perineural spread can be seen in this type of BCC as well. The infiltrative pattern in morpheaform BCCs does not show the typical stromal retraction or prominent peripheral palisading as seen in nodular BCCs. This histologic pattern explains why morpheaform BCCs commonly extend beyond the clinically visible area of the lesion and, therefore, traditional surgical excision without histological examination of the surgical margins may not remove the entire lesion and result in recurrence. Basosquamous BCCs, also called metatypical BCCs, have histological features that share those of BCCs and SCCs as a consequence of foci of squamous differentiation.

### 11.1.3 General Therapeutic Outline

Numerous treatment modalities are available for BCCs. Clinical treatment strategies vary in different countries. It is important for the physician to be familiar
with the current concepts of established treatment modalities for NMSCs and to individualize therapy for each patient. Due to the locally destructive growth pattern of BCCs, treatment is aimed at complete local eradication of tumor cells and cure. At the same time, maximal preservation of unaffected adjacent skin is desired to obtain the best possible cosmetic result.

The National Comprehensive Cancer Network (NCCN) in the United States has provided practice guidelines for the treatment of BCCs (http://www.nccn.org). Classification of BCCs as low-risk and high-risk is based on the clinical history of the lesion, a complete physical examination, a skin biopsy, and in case of extensive disease imaging studies. Risk factors...
for recurrence are determined based on the size and anatomic location of the lesion; whether it is primary or recurrent; whether the site has been exposed to ionizing radiation, and whether the patient is immunosuppressed. A high-risk lesion is defined as a BCC of at least 2 cm on the trunk and extremities, at least 1 cm on the cheeks, forehead, scalp or neck, or an area of at least 6 mm on the central face, periorbital, nose, genitalia, hands and feet. Poorly defined borders and recurrence put a BCC in the high-risk category. Prior radiotherapy to a lesion or immunosuppression also establishes a high-risk BCC. In addition, histological features are taken into consideration. While superficial and nodular BCCs are considered low-risk histological subtypes, a BCC with an aggressive growth pattern (including morpheaform, sclerosing, mixed infiltrative, or micronodular features in any portion of the tumor) is considered a high-risk BCC. According to the NCCN guidelines any single high-risk factor places the patient in the high-risk category.

Treatment guidelines for low-risk BCCs are as follows: (1) Curettage and electrodesiccation is appropriate for lesions in non-hair bearing areas that have not extended into the subcutaneous fat. (2) Surgical excision with 4 mm clinical margins and postoperative margin assessment. If the margins are positive, Mohs micrographic surgery is recommended (or complete circumferential peripheral and deep margin assessment with frozen or permanent sections). For lesions on the trunk and extremities with positive margins re-excision may be considered. (3) Radiation therapy may be an alternative approach for lesions with positive margins or as a primary treatment for non-surgical candidates.

Treatment guidelines for high-risk BCCs are as follows: (1) BCCs that are at least 2 cm in size on the trunk or extremities should be excised with a 1 cm clinical margin. If the margins are positive, Mohs micrographic surgery or radiation therapy is recommended. (2) Mohs micrographic surgery is recommended for all other high-risk BCCs. If negative margins are not achievable by the Mohs procedure, radiation therapy is recommended. If extensive perineural involvement is present, adjuvant radiation therapy should be considered. (3) Radiation therapy is an alternative treatment approach for patients not suitable for surgical intervention. Thus, curettage and electrodesiccation or cryosurgery are not recommended treatment options for high-risk BCCs.

Whatever modality is employed, the patient should have a complete skin examination every 6–12 months. Any locally recurring lesion is considered high-risk and must be managed as such. In the rare cases of distant recurrence, a multidisciplinary approach is recommended. The NCCN guidelines also recommend topical non-surgical approaches for superficial BCCs, where surgery or radiation therapy is either contraindicated or impractical. Generally, the cure rates for such modalities are lower than those for surgical treatments. Topical treatment options include 5-fluorouracil, imiquimod, photodynamic therapy or cryotherapy.

### 11.1.4 Current Established Therapies

Recurrence rates for BCCs as reported in a comprehensive study of 5,755 BCCs followed over a time period of almost 30 years showed that the 5-year recurrence rates were lower in primary BCCs as compared to recurrent BCCs (10.6% vs. 15.4%) (37). The risk of recurrence of treated primary BCCs was highest in the first 4 years after treatment.

With curettage and electrodesiccation of BCCs of all sizes on the trunk or extremities, 5-year recurrence rates were only 3.3%. BCCs on high-risk sites (nose, paranasal, naso-labial groove, ear, chin, mandibular, perioral, and periorcular areas) that had a diameter of less than 6 mm had a recurrence rate of 4.5% [96]. Risk factors for high recurrence rates included increasing lesion diameter, and location of the BCC on the head.

The cumulative 5-year recurrence rate after surgical excision of primary BCCs was 4.8% in this study. Risk factors for recurrence were male gender and location of the BCC on the head. While the 5-year recurrence rate of excised primary BCCs on the trunk and extremities was extremely low (0.7%), BCCs on the head showed increased recurrence rates with increased BCC tumor size (BCCs of at least 1cm diameter had a 9% 5-year recurrence rate) [97].

As part of the same study, 5-year recurrence rates were also assessed for BCCs that were treated with radiation therapy. Recurrence rates of 7.4% were seen in primary BCCs and 9.5% in recurrent lesions. BCCs on the head less than 1 cm in diameter had a 5-year recurrence rate of 4.4%, whereas lesions greater than 1 cm had a 9.5% recurrence rate. However, the long-term cosmetic outcome was significantly less favorable (61% with good cosmetic result) than with curettage and electrodesiccation (91%) or with surgical excision.
Mohs micrographic surgery for facial BCCs is performed more frequently in the United States than in most European countries. However, a recent retrospective study from The Netherlands concluded that Mohs micrographic surgery provides the lowest recurrence rates and is the treatment of choice for primary facial BCCs with an aggressive histopathological subtype and for recurrent facial BCCs, with 5-year recurrence rates for primary BCCs of 3.2% and for recurrent lesions of 6.7% [100]. This study was followed by a prospective randomized controlled trial comparing traditional surgical excision versus Mohs micrographic surgery for treatment of BCCs of the face. During a follow-up period of 30 months, 3% of primary BCCs recurred after traditional surgical excision, whereas 2% recurred after Mohs micrographic surgery. For recurrent BCCs, 3% recurred after traditional surgical excision while none recurred after Mohs micrographic surgery during an 18 months follow-up period. Because of the relatively short follow-up period no definitive conclusions can be drawn from this study [99]. These and other studies have questioned whether Mohs micrographic surgery of facial BCCs is cost-effective when compared to traditional surgical excision [24].

In a recent publication, a prospective multicenter case series included all patients with BCC (11,127) in Australia treated with Mohs micrographic surgery between 1993 and 2002. The vast majority of the BCCs occurred on the head and neck area (98.3%), and 43.8% were recurrent [58]. Of the patients in this study, 3,370 patients were followed for 5-years. The 5-year recurrence rate for primary BCCs was 1.4% and for recurrent BCCs 4% [59]. Five-year recurrence rate for BCCs with perineural invasion was 7.7% [57]. Thus, the Australian experience with Mohs micrographic surgery for facial BCCs has been very favorable for this treatment approach.

A systematic review of published studies on the treatment modalities for BCCs showed that Mohs micrographic surgery has the lowest 5-year recurrence rates, although most studies could not be compared directly [116]. In addition, this review concluded that most studies found higher 5-year recurrence rates with curettage and electrodesiccation compared to surgical excision (5.7–18.8% versus 3.2–8.0%) [116].

Alternative treatment options include the use of the topical immune response modifier imiquimod, which has been approved for the treatment of superficial BCCs in the United States, Europe and Australia. It acts as a Toll-like receptor-7 (TLR7) agonist, inducing cytokines such as interferon-α through the innate immune system and stimulating T-cell mediated immunity. A tumorcidal activity of TLR7-activated inflammatory dendritic cells has recently been reported [104]. However, the molecular mechanisms whereby imiquimod inhibits tumor cell growth are only partially understood. Recent evidence suggests that imiquimod may stimulate Notch signaling in superficial BCCs [126], while loss of Notch signaling has been implicated in the development of BCCs associated with increased expression of Gli2 of the Shh signaling pathway [73, 115].

Imiquimod has been approved for the treatment of biopsy-proven primary superficial BCCs that are less than 2 cm in size and that are located on the trunk, neck and extremities of immunocompetent adults. Treatment of superficial BCCs with topical imiquimod 5x/week for 6 weeks resulted in histologically confirmed cure 12 weeks after treatment in 82% of cases [28], while daily application was no more efficacious. Similar results were found in a multicenter study in Europe, in which patients with superficial BCCs were treated with daily applications of imiquimod for 6 weeks. Histological clearance was documented after 12 weeks in 80% of patients (versus 6% in patients treated with vehicle alone) [93]. An Australian study showed a clinical clearance rate at 12 weeks post treatment of 94%, which fell to 82% after 2 years [84]. Similar interim results at 2 years post treatment were reported from a study in Europe [29].

Nodular BCCs are much less responsive to topical imiquimod treatment. In a small study, 93% of superficial BCCs treated with topical imiquimod (3x/week for up to 12 weeks) showed a complete clinical response whereas 53% of nodular BCCs responded [80]. These results have been duplicated in other studies [106]. Thus, topical imiquimod should be used only for superficial BCCs, not for nodular or morpheaform lesions.

Preliminary studies suggest a possible benefit in combining topical imiquimod with curettage of BCCs [90]. These results will require further analysis.

Topical photodynamic therapy (PDT) using 5-aminolevulinic acid (ALA) or methyl aminolevulinate...
(MAL) represents an additional non-invasive option for the treatment of BCCs. Photoactivation of these photosensitizers results in cytotoxicity through generation of reactive oxygen species. It is believed that there may be some degree of selectivity of tumor cells relative to adjacent non-neoplastic cells to PDT after topical ALA or MAL application.

While ALA has been mainly marketed in the United States and Canada for topical PDT, MAL has been marketed in Australia, New Zealand and Europe. To maximize cytotoxicity on neoplastic cells, the duration of application of MAL and ALA has to be chosen appropriately as well as the light source. Blue light has been used successfully for the treatment of thin AKs. However, red light penetrates more deeply into the skin and is therefore more beneficial in the treatment of BCCs.

Good response rates were observed with topical PDT treatment of superficial BCCs and thin nodular BCCs. An international consensus on the use of topical PDT for BCCs has recently been published [9]. Multiple studies, using either ALA-PDT or MAL-PDT showed initial clearance rates often above 90% for superficial BCCs with favorable cosmetic results, but with relatively high recurrence rates. One European multicenter study of MAL-PDT for difficult-to-treat BCCs (lesion location or size), histological remission at 3 months was achieved in 85% of superficial BCCs; in 75% of nodular BCCs, but only in 43% of mixed thin AKs. Two year-follow-up showed an overall recurrence rate of 18%, and the cosmetic outcome was graded as excellent or good for 94% of treated lesions [37]. Another study compared the recurrence rates of nodular BCCs treated with surgical excision or with topical MAL-PDT [88]. Five years after treatment, 14% of nodular BCCs treated with topical MAL-PDT recurred, whereas only 4% of surgically excised nodular BCCs recurred. A good or excellent cosmetic outcome was reported for 87% of patients treated with MAL-PDT, but only for 54% of surgically treated patients. These data support the concept that rapid PDT is a useful alternative to surgery in certain patients with BCCs who are not good surgical candidates.

Comparison of ALA-PDT with cryosurgery for treating BCCs showed similarly high recurrence rates for both at 12 months after treatment, 25% for ALA-PDT and 15% for cryosurgery. Healing time was shorter and cosmetic outcome was better with PDT than with cryosurgery [122].

In conclusion, topical PDT is a useful option for large or multiple superficial BCCs, and generally gives a good to excellent cosmetic result. PDT can also be used for nodular BCCs less than 2 mm in depth. MAL-PDT is approved for nodular BCCs in Europe, Australia, New Zealand and Brazil. Thicker BCCs can be surgically debulked prior to using PDT. MAL-PDT may be superior to ALA-PDT in managing nodular BCCs due to better tissue penetration of MAL [78]. However, a study in which superficial BCCs were treated with ALA-PDT and visible light, dermal fibrosis reached deeper into the dermis than the initial BCC. Thus, the authors concluded that the relatively high 5-year recurrence rates (with only 50% disease-free 5 years later) could not be explained by insufficient tissue penetration of ALA [26].

11.1.5 Experimental Approaches

In mouse studies, immunization with proteins that are specifically up-regulated by Shh signaling led to a decrease in the number of BCCs induced with ionizing radiation in Patch1+/− mice [120]. This study shows the potential for immunotherapy of BCCs.

In mutant mouse models it has been demonstrated that cutaneous ornithine decarboxylase, the first enzyme in the polyamine-biosynthesis pathway that drives cell proliferation, is essential for the growth of BCCs. Oral administration of α-difluoromethylornithine, an ornithine decarboxylase inhibitor, reduced UVB-induced BCCs in Patch1+/− mice [111]. This study demonstrates that chemopreventive strategies may be applicable in the prevention of BCCs.

Similarly, topical administration of the retinoid tazarotene inhibited BCC formation in Patch1+/− mice susceptible to the induction of BCCs when treated with either UV or ionizing radiation [102]. The concept of using topical retinoids to treat BCCs stems from the observation that orally administered retinoids at high doses may inhibit the growth of BCCs in high-risk populations, such as in patients with the nevoid BCC syndrome, with xeroderma pigmentosum or immunosuppressed organ transplant recipients [72, 77]. In preliminary studies, it was suggested that topical tazarotene has some benefit in the treatment of human BCCs, although the remission rates were not comparable to currently established treatment options [6, 79]. Thus,
topical tazarotene may have a benefit in the chemoprevention of BCCs rather than in the treatment of already formed tumors.

Finally, experimental approaches to increase the efficacy of established treatment options are being evaluated. For example, an iron-chelating agent was added to ALA to enhance intratumoral porphyrin accumulation during topical PDT of nodular BCCs [15]. This preliminary study showed improved clearance rates, but larger studies will be necessary to determine the clinical value of this approach.

11.1.6 SCC

11.1.6.1 Etiology and Pathophysiology

SCCs are NMSCs that manifest distinct differences as compared to BCCs in their clinical and biological behavior. SCCs appear to progress along a multi-step carcinogenesis pathway: they can evolve from precursor lesions (AKs), progress to full-thickness epidermal dysplasia (SCC in situ), and eventually can become aggressive (invasive SCC) and metastasize. Once SCC metastasis has occurred, the prognosis is very poor with less than 10% 10-year survival. Cumulative UV irradiation through chronic sun-exposure is thought to be important in the pathogenesis of SCCs. Photocarcinogenesis describes a continuum that begins with the induction of mutations in the p53 tumor suppressor gene by UV irradiation, enabling keratinocytes to escape apoptosis and undergo clonal expansion. Over time additional mutations accumulate due to continued UV exposure, which promote the acquisition of more invasive growth behavior of premalignant keratinocytes, eventually forming a fully malignant SCC cell clone. This multi-step carcinogenesis model for SCC development has led to the concept that treatment of such “precursor” lesions of SCCs, namely actinic keratoses and SCCs in situ (Bowen’s disease), may prevent the development of fully malignant keratinocyte cell clones that result in invasive SCCs.

An important role of p53 tumor suppressor gene mutations in photocarcinogenesis has been shown in many studies. Sunlight exposure induces the expression of p53, which acts as a tumor suppressor by increasing DNA repair or arresting the cell cycle and inducing apoptosis in UV-damaged cells. Through these functions p53 prevents the clonal expansion of atypical keratinocytes. p53 mutations in keratinocytes make them more resistant to p53-induced apoptosis [10]. This was demonstrated in murine skin by means of genetic inactivation of p53, which resulted in a reduction of UV-induced apoptotic keratinocytes, so-called sunburn cells [134].

When SKH-1 hairless mice were irradiated with UVB, epidermal patches formed in which keratinocytes harbored p53 mutations that closely mimic those seen in UVB-induced SCCs in mice, suggesting that the UVB-induced patches with p53 mutations are direct precursor lesions of SCCs [49, 62]. Mutational analysis of the p53 gene revealed so-called ‘UV signature’ mutations, being single or tandem transitions at dipyrimidine sequences in the DNA-binding domain of the p53 gene (C to T and CC to TT transitions). Irradiation of SKH-1 hairless mice with UVB verified delayed development of SCCs from precursor lesions when irradiation was discontinued, supporting the concept that chronic UV-irradiation is a major factor in the pathogenesis of SCCs [66]. Application of sunscreen to mice prior to UVB-irradiation substantially reduced p53 signature mutations and they formed fewer tumors than animals receiving no sunscreen [1].

Further evidence for an important role of UV-induced p53 gene mutations in the pathogenesis of NMSCs stems from UVB-induced carcinogenesis experiments in mice that received a small molecular weight compound capable of restoring wild type p53 functionality, resulting in diminished tumor induction [112]. Identification of mutations in the p53 gene may also have prognostic value clinically. Patients with SCCs of the head and neck were found to have a reduced survival if their SCCs had p53 mutations [82].

p53 appears to have additional functions in the skin beyond its role as a tumor suppressor. It has recently been shown that UV-induced pigmentation via α-melanocyte-stimulating hormone (α-MSH) is directly controlled by p53, demonstrating that this tumor suppressor also has an essential role in the suntan response [20].

In addition to the mutagenic effects of UV-radiation, it has been proposed that it promotes NMSCs through suppression of antitumoral immune responses. UV-irradiation, in particular in the UVB spectrum, induces antigen-specific immune tolerance via regulatory T-cells. Induction of regulatory T-cells requires antigen-presentation by Langerhans cells. Regulatory T-cells have been characterized as being CD4+ and
CD25+, which upon activation release the immunosuppressive cytokine interleukin-10 (IL-10). Thus, antigen-specific activation of regulatory T-cells can lead to an immunosuppression via IL-10, which is known to suppress T-helper(h)-1 cells [5]. In the absence of UV-irradiation, epidermal antigen-presenting cells present tumor-associated antigens to induce protective immunity.

The importance of IL-10 release for promoting the growth of cutaneous malignancies was shown in mutant mice lacking IL-10, which had significantly fewer NMSCs after UV-irradiation than did wild-type mice [61]. Thus, UV-irradiation inhibits antitumor immunity via IL-10. In addition, these data demonstrate the importance of Th1 cell responses and of UV-induced regulatory T-cells for growth inhibition of NMSCs.

Further evidence for the importance of the immune system in protecting against UV-induced NMSCs has emerged from the observation that organ transplant recipients who require chronic treatment with immunosuppressive drugs are at high risk for the development of NMSCs, particularly aggressive SCCs.

Clinical and histological characteristics of SCCs provide further evidence for chronic UV-irradiation as a major factor in SCC pathogenesis: first, SCCs are mainly located on anatomic areas that are directly exposed to sunlight, such as the hairless scalp, the face, the ears, and the dorsal hands; and second, UV-induced histologic changes, such as solar elastosis, can be seen in biopsies from SCCs or its precursor lesions.

However, the individual risk that a precancerous skin lesion will progress to an invasive SCC is rather low, and most precancerous skin lesions are likely to remain stable or regress.

NMSC rates increase with tanning lamp usage, and this is particularly the case for SCCs [43]. Therapeutic UV-irradiation may also contribute to NMSC development. Psoriasis patients who have been treated with long-term UVB and PUVA therapy are at higher risk for developing SCCs, which is likely due to the combination of increased UV-exposure and the associated cutaneous immunosuppression [42, 105]. It is of interest that PUVA therapy appears to drive the growth of SCCs to a greater extent than ofBCCs. In contrast, radiation therapy is associated with BCCs and not SCCs, particularly in sun-sensitive, fair-skinned patients [42].

Exposures to certain chemicals have also been linked to the development of NMSCs, especially SCCs. Chronic exposure to arsenic, polycyclic aromatic hydrocarbons, tar, asphalt and certain pesticides has been linked to the growth of NMSCs.

In addition to the increased NMSC risk in organ transplant recipients, patients with HIV infection appear to develop human papillomavirus (HPV)-related SCCs of the anus with increased frequency.

HPVs, particularly subtypes 5 and 8, may be associated with verrucous SCCs as well as with some SCCs as well as some SCCs in organ transplant recipients [44, 75].

Finally, certain genodermatoses have been associated with NMSCs. Increased incidences of SCCs have been reported in genodermatoses with impaired DNA repair mechanisms, pigmentation defects or chronic infections. These include xeroderma pigmentosum, albinism, epidermodysplasia verruciformis, and dystrophic epidermolysis bullosa.

11.1.6.2 Clinical Characteristics and Diagnosis

11.1.6.2.1 Actinic Keratosis

Actinic keratoses (AKs) occur predominantly on sun-exposed areas in elderly patients, particularly on the hairless scalp, the face, the ears, and the dorsal hands. They are most common in fair-skinned sun-sensitive patients with a history of chronic sun exposure. They appear typically as erythematous scaly papules or plaques, which may be tender and can often be distinguished from adjacent clinically uninvolved skin by palpation of the overlying scale. AKs form in skin areas that usually manifest signs of photoaging. Clinically, various subtypes of AKs have been described, including hyperplastic (hyperkeratotic), pigmented, lichenoid, atrophic, or Bowenoid types. AKs may occasionally manifest as cutaneous horns, which may evolve into SCCs. AKs are thought to be precursors to SCCs, but the risk of progression is thought to be low (<0.10% annually). However, in a patient with multiple AKs the risk of developing an SCC is greater if the AKs are left untreated.

Histopathological examination of SCCs demonstrated that 82.4% of lesions were in close proximity to AKs, with 26.7% of SCCs arising in AKs [68]. Such
observations have led to the proposal that AKs may be early SCCs in situ [91].

The diagnosis of AKs can usually be made clinically although histological confirmation may sometimes be necessary. Histologic features include crowding of atypical keratinocytes in the basal layer of the epidermis as well as parakeratosis that often spares the adnexa, leading to the histological picture of alternating ortho- and parakeratosis (so-called ‘flag sign’). Dermal solar elastosis is prominent, as AKs form in chronically sun-damaged skin (Fig. 11.1.5a and b).

11.1.6.2.2 SCC In situ (Bowen’s Disease)

Clinically, SCC in situ presents as an erythematous scaly plaque, seen in sun-damaged skin areas of older patients (Fig. 11.1.4b and c). SCCs in situ can arise in AKs, or may form de novo. These lesions are commonly biopsied, since the clinical differential is broad and includes nummular eczema, superficial BCC or psoriasis. Immunocompromised patients are more likely to form multiple SCCs in situ, have a higher rate of recurrence, and their lesions can be found with higher frequency on the trunk, the extremities and the neck [23].

There are several clinical variants of SCC in situ. Arsenic-induced SCCs in situ are often multifocal and may arise in skin areas that are not sun-exposed, consistent with a chemical as compared to a UV-induced pathogenesis. Characteristically, arsenic exposure leads also to palmoplantar keratoses and pigmentary changes (mottled hyperpigmentation with areas of hypopigmentation).

Bowenoid papulosis presents clinically as reddish-brown papules on the skin of the external genitalia and the perianal region in young adults (Fig. 11.1.4h). These lesions are often infected by oncogenic HPV strains (particularly HPV-16 and HPV-18), and may be a variant of SCC in situ, mainly because of similar histological findings. However, in this anatomic location they rarely evolve into invasive SCCs.

SCC in situ of the mucosal surfaces of the penis in uncircumcised males is known as erythroplasia of Queyrat, which may progress to an invasive SCC.

Histologically, SCC in situ is characterized by a full-thickness epidermal dysplasia that shows mitotic figures and dysplasia along the adnexal structures (Fig. 11.1.5d).

11.1.6.2.3 Invasive SCC

Progression of SCC in situ to an invasive SCC is often associated with increasing tenderness at the site of the lesion, hyperkeratosis may become more prominent, and the lesion may become more nodular or even ulcerate (Fig. 11.1.4d and f). In general, the rate of metastasis from SCCs in sun-damaged skin is low. Certain clinical settings are associated with higher risk of metastasis. SCCs of the ear and lip and tumors that arise in chronic wounds or at sites of chronic inflammation carry a higher risk of metastasis. Immunosuppressed organ transplant recipients have an increased risk of metastasis as well. While the rate of BCC formation may increase ten-fold in organ transplant recipients, SCCs increase by a factor of 65–250 in these patients [25]. SCCs in organ transplant recipients frequently occur in previously sun-exposed sites with chronic photodamage. The frequency of SCC occurrence in these patients correlates with the extent of immunosuppression. In addition, certain immunosuppressive medications have been implicated to contribute to NMSC formation more than others and via direct cellular effects on keratinocytes in addition to their immunosuppressive effects. While cyclosporine may promote NMSC via inhibition of DNA repair and apoptosis after UVB-irradiation [129], inhibitors of mTOR signaling, such as sirolimus (rapamycin), appear less likely to enhance the growth of NMSCs in organ transplant recipients despite achieving a degree of immunosuppression that avoids graft rejection [16, 30].

Invasive SCCs manifest varying degrees of differentiation histologically. Nuclear atypia increases with decreasing differentiation of invasive SCCs (Fig. 11.1.5g). Poorly differentiated SCCs may appear as spindle cell tumors that lack keratinization, and may require immunohistochemical differentiation from spindle-cell melanoma, leiomyosarcoma or other histologically similar lesions (Fig. 11.1.5h). Acantholytic or adenoid variants can occur (Fig. 11.1.5e and f). It is important to assess for perineural invasion, which is associated with a more aggressive phenotype.

On the other hand, verrucous SCCs usually grow locally and metastasize infrequently (Fig. 11.1.4e and g). Verrucous carcinoma of the planter surface is known as epitheliomacuniculatum; of the anogenital area as giant condyloma of Buschke-Lowenstein, and of the mouth as oral florid papillomatosis. Another variant of a well-differentiated SCC with mild atypia is keratoacanthoma (Fig. 11.1.5c), which usually presents as a rapidly growing crateriform papule/nodule/tumor that typically
grows rapidly over a period of weeks and then may regress spontaneously (Fig. 11.1.4a).

11.1.6.3 General Therapeutic Outline

The NCCN has developed treatment guidelines for SCCs. Treatment options are defined by the aggressiveness of the tumor. Locally growing lesions with no evidence for metastasis require categorization into low-risk or high-risk. The NCCN criteria include clinical as well as histopathologic features.

In terms of location and size, a high-risk SCC is defined (according to NCCN criteria) as being at least 2 cm in size when located on the trunk or extremities; at least 1 cm in size when located on the cheeks, forehead,
Fig. 11.1.5 Histology of atypical squamous cell lesions. (a) AK with alternating ortho- and parakeratosis and extensive solar elastosis in the dermis (×10). (b) Hyperkeratotic AK (×10). (c) Keratoacanthoma shows a central crater filled by cornified material in its core (×10). (d) SCC in situ with epidermal full-thickness atypia and multiple mitotic figures (×20). (e) Acantholytic SCC (×4). (f) Acantholytic SCC with acantholytic cells within squamous tumor islands that extend from the epidermis (×20). (g) Invasive SCC with brightly eosinophilic atypical keratinocytes forming tumor strands that extend from the epidermis (×20). (h) Spindle cell-type invasive SCC with elongated atypical appearance of tumor cells (×20).

scalp or neck, or at least 6 mm in size when located in the “mask areas” of the face (central face, eyelids, eyebrows, periorbital region, nose, lips, chin, mandible, pre- and postauricular areas, temple, and ear) or the genitalia or hands and feet. However, under some circumstances lesions smaller than 6 mm occurring in these areas may constitute high-risk lesions. Additional features of high-risk lesions include poorly defined borders; recurrence, and growth at the site of prior radiation therapy or at the site of chronic inflammation or wounding. Additional high-risk lesions include those in immunosuppressed patients and those with evidence of perineural spread. Histopathologic criteria that constitute a high-risk SCC are (1) a moderate or poor differentiation, (2) adenoid
11.1 Nonmelanoma Skin Cancer

(acellularytic), adenosquamous (showing mucin production), or desmoplastic subtypes, (3) deep vertical growth pattern (Clark level IV or V or a thickness of at least 4 mm), (4) perineural or vascular involvement.

The goals of primary treatment of SCCs are cure of the tumor, while preserving anatomical function and cosmesis. For low-risk SCCs in non-hair-bearing areas curettage and electrodesiccation may be performed. Alternatively, surgical excision with a 4–6 mm clinical margin is indicated. If however, margins of the surgical specimen are positive for SCC, Mohs micrographic surgery is indicated, or re-excision if the lesion was present on the trunk or extremities. Radiation therapy is reserved for non-surgical candidates. In patients with low-risk SCCs in situ, in whom surgical treatments or radiation is contraindicated, topical treatment alternatives may be considered. These include the use of 5-fluorouracil, imiquimod, PDT, or cryotherapy.

In contrast, high-risk SCCs should be surgically excised. If the SCC is at least 2 cm in size, SCCs on the trunk or extremities should ideally be removed with 1 cm clinical margins. Where such a margin is not practical (for example for SCCs of the face) Mohs micrographic surgery is indicated. In cases with extensive perineural involvement adjunctive radiation therapy may be indicated. Radiation therapy is also an important option in cases in which histologically negative surgical margins are not achievable.

Particular attention should be paid to performing a careful lymph node examination in patients with high-risk SCCs. Enlarged regional lymph nodes require histological examination. Lymph node involvement necessitates regional lymph node dissection, and radiation therapy should be considered for patients with a high-risk for regional recurrence.

Radiation therapy is also an important option for satellite lesions (in-transit metastases) [34], although controlled prospective clinical studies are needed to determine its efficacy. However, well-differentiated SCC-type lesions such as verrucous carcinoma and keratoacanthoma are not appropriate for radiation therapy, since this may promote cellular transformation to a more aggressive SCC.

More frequent clinical follow-up examinations are recommended for high-risk lesions. While patients with a treated low-risk SCC should be examined every 3–6 months during the first 2 years following treatment, then every 6–12 months for 3 years and thereafter annually, patients with a treated high-risk SCC should be examined every 3 months for 2 years, then every 4 months for 1 year, then every 6 months for 2 years, and annually thereafter (according to NCCN recommendations).

These NCCN guidelines provide general treatment recommendations, but in clinical practice treatment and follow-up need to be individualized according to the clinical characteristics of each SCC and the identifiable risk factors present in each patient (e.g., immunosuppressive therapy, genodermatoses that predispose to cancer, such as xeroderma pigmentosum).

11.1.6.4 Current Established Therapies

11.1.6.4.1 Preventive Treatments

Since SCCs appear to evolve along a multi-step carcinogenesis pathway that starts with precancerous lesions, it is recommended that these lesions (AKs and SCCs in situ) be treated early. Established treatment options include liquid nitrogen cryosurgery, topical 5-fluorouracil (5-FU), topical imiquimod, PDT, or curettage and electrodesiccation. This concept also provides the basis for preventive treatment approaches in high-risk patient populations, such as organ transplant recipients. Oral retinoids (acitretin, isotretinoin) have been shown to slow the growth of SCCs in high-risk patient populations, although therapeutic benefit ceases if the drugs are discontinued. A 16-year retrospective study from England assessed the effects of chronic low-dose oral retinoid treatment on the growth of SCCs in organ transplant recipients [36]. Chronic low-dose treatment with oral retinoids reduced incidence rates and discontinuation of therapy led to a rebound increase in SCCs. Retinoid side-effects, including headaches, hyperlipidemia, pruritic rashes and musculoskeletal symptoms limited acceptance of these drugs in many patients [18].

11.1.6.4.2 Topical Treatment of SCCs or Precursor Lesions

Imiquimod has been approved for the treatment of AKs in the United States, used as a topical cream applied 2–3x/week over 16 weeks. A complete clinical clearance
rate of 48.3% of AKs treated 3x/week for 16 weeks was reported in a study conducted in the United States [48]. A similar study in several European centers reported a clearance rate of 57.1% with this treatment regimen [108, 110]. The initial and 12-month clearance rates for AKs treated with either 5% 5-FU ointment (twice daily for 4 weeks), 5% imiquimod cream (one or two courses of 3x/week for 4 weeks each) or cryotherapy were compared [50]. Histological clearance rates were 32% after cryotherapy, 67% after 5-FU treatment, and 73% after imiquimod treatment. Imiquimod yielded the best cosmetic results. Other studies have shown that 5-FU is more effective than imiquimod. Complete clearance of treated AKs was seen at week 24 in 84% of the 5-FU group, but in only 24% of the imiquimod group [114].

Notably, imiquimod is also effective for treating AKs in organ transplant recipients [118]. SCCs in situ also respond to topical imiquimod. In a small study, daily application of 5% imiquimod cream for 16 weeks to SCCs in situ resulted in clinical clearance in 73% of patients, although the follow-up period was only 9 months in this study [76]. Good response rates of SCCs in situ on the legs were also reported in a study from Australia [63]. Notably, some studies also report regression of invasive SCCs after topical imiquimod treatment [81]. However, topical imiquimod therapy is not appropriate for invasive SCCs.

The most common treatment modality for AKs is cryotherapy, with response rates typically greater than 75%, but with annual recurrence rates of up to 12% [107]. A clinical study compared cryotherapy with MAL-PDT in the treatment of AKs (excluding facial and scalp AKs) in an intraindividual right-left comparison [46]. At 24 weeks, mean percentage reduction in lesion count was 88% for cryotherapy and 78% for MAL-PDT, although cosmetic outcome was superior in the PDT group.

MAL-PDT has also been evaluated in the treatment of SCCs in situ and invasive SCCs [14]. The overall complete response rate at 2 years was 53.6%, with the extent of cellular atypia being an independent predictor of treatment outcome. MAL-PDT is useful in patients with superficial, well-differentiated SCCs in situ or microinvasive SCCs, but not so for poorly differentiated SCCs. Nonetheless, PDT is an alternative for AKs and SCCs in situ [9].

A retrospective review of patients with SCCs in situ treated with various modalities at one center in the United States showed that 5-year recurrence rates were highest for lesions treated with cryotherapy (13.4%), followed by topical 5-FU (9%) and shave excision (9%). In contrast, 5-year recurrence rates were lower if the lesions were treated with electrodesiccation and curettage (6.5%), Mohs micrographic surgery (6.3%) or elliptical excision (5.5%) [35]. Low-risk SCCs may respond to cryosurgery [52]. Surgical Treatments

Mohs micrographic surgery is an efficacious, cost-effective and safe procedure for high-risk SCCs [113, 114]. Curettage prior to surgical excision of NMSCs may aid in defining subclinical tumor margins and reduce the risk of incomplete excision particularly for BCCs, but not SCCs [19, 86]. Mohs micrographic surgery has the highest 5-year cure rate for primary SCCs (over 95%) when compared with other treatment modalities. This difference becomes even more significant when treatment modalities for recurrent SCCs are compared [92].

A 5-year follow-up study assessed recurrence of NMSCs of the external ear that were treated with curettage followed by cryosurgery with liquid nitrogen [74]. Results showed a very low recurrence rate, demonstrating that curettage-cryosurgery is a treatment alternative for NMSCs in this location. Similarly, curettage combined with electrodesiccation has 5-year cure rates of over 90% for low-risk SCCs.

This treatment modality is also recommended for the treatment of otherwise low-risk SCCs (based on size and anatomic location) in immunosuppressed organ transplant recipients [21].

A disadvantage of locally destructive procedures compared to Mohs micrographic surgery is the lack of histologic assessment of surgical margins, which makes Mohs micrographic surgery the treatment of choice particularly for high-risk SCCs [92]. In a study from Australia, 5-year recurrence rates for NMSCs of the scalp that were treated with cryosurgery were only 3.2% for SCCs and 5.7% for BCCs [60]. However, 5-year recurrence rates for primary SCCs were even lower (2.6%) compared to recurrent SCCs (5.9%) [54]. Even NMSCs at high-risk locations had a very low 5-year recurrence rate when treated with Mohs micrographic surgery [56]. Perineural invasion of SCCs is associated with higher 5-year recurrence rates even when treated with Mohs micrographic surgery followed by Radiation therapy [55].

Radiation therapy is indicated in patients who have high surgical risk factors. Radiotherapy of NMSC of
the pinna showed a 5-year cure rate of 78%, well below the cure rates achieved with Mohs micrographic surgery or excisional surgery [13]. Further disadvantages of radiation therapy are the need for multiple treatments, and evidence that recurrences may be more aggressive. Thus, high-risk aggressive primary SCCs should be treated surgically if possible. Radiation therapy has an important role in the adjuvant treatment of metastatic SCCs to lymph nodes in the head and neck area, improving the 5-year disease-free survival rate significantly [119].

**11.1.6.5 Experimental Approaches**

Several experimental drugs and compounds have been tested in mouse models for their role in preventing or reducing the growth of SCCs. Plant-derived isoflavones, such as genistein extracted from soybeans, may have a role in the prevention and treatment of SCCs. Chemical carcinogenesis and photocarcinogenesis experiments in mouse models showed delayed SCC formation in mice that received topical treatment with the isoflavone equol [125]. In vitro experiments demonstrated that genistein decreased proliferation of a SCC cell line and reduced prostaglandin E2 (PGE2) levels through inhibition of cyclooxygenase-2 (COX-2) activity [130]. It has been proposed that increased PGE2 through upregulated COX-2 expression has proinflammatory effects that contribute to SCC progression. Prostanoid receptors, which bind PGE2, are overexpressed in SCCs, but not in BCCs or normal skin, supporting a role for PGE2 in SCC formation [53]. Moreover, inhibition of COX-2 with nimesulide reduced UVB-induced photocarcinogenesis in a mouse model [113]. Similarly, the COX-2 inhibitor celecoxib was shown to inhibit SCC formation [131]. Clinical studies provided evidence in support of a therapeutic effect of topically applied COX-inhibitors in the treatment of AKs. Topical application of 3% diclofenac sodium gel for 90 days resulted in significant clearance of AKs [71]. This drug is FDA-approved in the United States for the treatment of AKs.

Naturally occurring compounds, such as resveratrol (found in the skin of grapes and other fruits), reduce SCCs in mouse models. Resveratrol was shown to inhibit cell proliferation in cancer cells directly [47]. In addition, topical application of resveratrol inhibited UVB-induced SCCs in mice [3]. Several studies also demonstrated that green tea extracts protect the skin against phototoxicity by inhibiting DNA damage and inflammation [123, 132].

Treatment of metastatic SCCs requires systemic chemotherapy, often including cisplatin, but the prognosis remains poor. Recently, a targeted treatment approach with cetuximab, a chimeric antibody against the epidermal growth factor receptor (EGFR), induced regression of metastatic SCCs [4]. This report demonstrates the importance of assessing the efficacy of novel therapeutic agents and that long-term follow-up examinations are needed to determine their cure rates.

**11.1.6.6 Complications to Avoid**

It is important to choose the appropriate treatment modality for each NMSC in order to maximize cure and minimize the risk of recurrence. At the same time, the importance of regular follow-up examinations of the treated patient must be emphasized. Surgical approaches can have complications that include hematoma formation, wound infection and wound dehiscence. Also, hypertrophic scarring and keloid formation can occur after surgical intervention. These may be minimized by close follow-up examinations after the procedure and with use of intraleisional triamcinolone acetonide injections where indicated.

Side effects of topical medical treatments are usually limited to local skin reactions. However, it is important to discuss the higher recurrence rates with these treatment approaches with the patient and to provide appropriate follow-up care.

**Take Home Message**

- The appropriate treatment of NMSCs depends on their classification as a low-risk or a high-risk lesion, based on size, anatomic location, histological variant and other clinical features. Thus, the optimal treatment approach has to be chosen not only for each patient individually, but also for each lesion separately. The aim of the treatment should be the complete removal of the NMSC to achieve cure. For high-risk lesions at anatomic sites where a
A. G. Marneros and D. R. Bickers

11.1.7 Global Variations

There are significant global variations in the treatments of NMSCs. These differences are influenced in part by the greatly varying incidences of NMSCs in different countries. Furthermore, treatment approaches are influenced by differences in health care systems and reimbursement practices that differ significantly in different countries. For example, Mohs micrographic surgery for the treatment of NMSCs is performed more commonly in the United States and Australia, while surgical excision is more common in Europe. The increase in established Mohs surgical fellowships in the United States and other countries has further promoted this trend. Nonetheless, treatment guidelines for NMSCs are similar globally [11, 12]. In addition, availability of certain topical treatments for NMSCs differs in various countries. For example, MAL-PDT has been used primarily in Europe and Australia, while ALA-PDT has been used mainly in the United States and Canada.

References


Malignant Melanoma

Toshiaki Saida

11.2.1 Epidemiology, Etiology and Pathogenesis

Malignant melanoma is a malignant neoplasm of melanocytes, which have the potential for melanin production, and thus, most melanomas are recognized as a brownish black lesion. There is big difference in incidence of malignant melanoma among races; number of new patients/100,000 persons/year is about 10–20 in white persons, less than one in black persons, and about two in Japanese. This difference is mainly due to the occurrence of a large number of melanomas affecting trunk and non-acral extremities in white populations. Acral melanoma is the most prevalent subtype in non-white populations and melanoma of this type shows unique morphological and genetic characteristics. Most malignant melanomas can be detected in early, curable stages, if we apply valid clinical and dermoscopic criteria for the diagnosis. Clinical guidelines for the management of cutaneous melanomas have been proposed in several countries, and we can obtain the latest information about the management via the Internet. Narrow surgical margins have been established in excising the primary lesions of melanoma. Particularly, melanoma in situ can be cured by simple excision with 3–5 mm free margin. Sentinel lymph node biopsy is becoming a standard procedure, instead of the elective lymph node dissection.

Key Features

- Incidence of malignant melanoma and proportions of its subtypes are markedly different among races. This is mainly due to extremely higher incidence of melanoma affecting trunk and non-acral extremities in white populations.
- Acral melanoma is the most prevalent subtype in non-white populations and melanoma of this type shows unique morphological and genetic characteristics.
- Most malignant melanomas can be detected in early, curable stages, if we apply valid clinical and dermoscopic criteria for the diagnosis.
- Clinical guidelines for the management of cutaneous melanomas have been proposed in several countries, and we can obtain the latest information about the management via the Internet.
- Narrow surgical margins have been established in excising the primary lesions of melanoma. Particularly, melanoma in situ can be cured by simple excision with 3–5 mm free margin. Sentinel lymph node biopsy is becoming a standard procedure, instead of the elective lymph node dissection.

Melanoma is resistant to chemotherapy and radiotherapy, and effective therapies for patients with advanced melanoma are yet to be established. Recent clinical and basic studies of melanoma have revealed dozens of innovative findings in various fields, which will contribute to establish revolutionary diagnostic and therapeutic modalities in the future.

T. Saida
Professor Emeritus, Department of Dermatology, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan
e-mail: tosaida@xb4.so-net.ne.jp

T. Krieg et al. (eds.), Therapy of Skin Diseases, DOI: 10.1007/978-3-540-78814-0_11.2, © Springer-Verlag Berlin Heidelberg 2010
adverse effect on skin when exposed to ultraviolet light [27]. However, recent study has revealed that the skin color is determined only by the amount of eumelanin [30]. Thus, lower eumelanin content in the skin could be the main causal factor of cutaneous melanoma in white persons. In addition, particular mutations in melanocortin-1 receptor (MC1R) gene have been revealed to be a major risk factor of melanoma development [52]. The risk seems to be independent of the melanin types [32].

The most prevalent site of melanomas in black persons is acral skin such as soles, palms, and nail-apparata. In Japanese, about 30% of all melanomas occur on the sole. It was reported that the absolute incidence of melanoma on acral skin is almost same among races [65]. Acral volar skin is hypopigmented even in black persons. This hypopigmentation could be a cause of the predilection of melanoma in acral volar skin. Reasons for the hypopigmentation in acral volar skin are yet to be clarified. Yamaguchi et al. have reported that the hypopigmentation of volar skin is due to inhibition of melanocyte through mesenchymal-epithelial interactions via increased dickkopf-1 derived from the dermal fibroblast of acral skin [70, 71]. Dickkopf-1 is an inhibitor of the Wnt signaling pathway. Our recent studies suggest that, in volar skin, endothelin-1(ET-1)/stem cell factor(SCF)/receptor-linkages are significantly down regulated, which will be responsible for the hypopigmentation [27]. Further studies are necessary to determine the precise mechanism of hypopigmentation in acral volar skin. In addition to the hypopigmentation, mechanical trauma could be another major factor for melanoma predilection to acral volar skin. The soles are far more frequently affected by this neoplasm than the palms, and the thumb is the most prevalent site of nail apparatus melanomas among all digits [29]. These data indicate that mechanical trauma plays an important role in the induction of melanoma in acral skin. Acral melanocytes may be more vulnerable to mechanical trauma because of melanin precursors contained in their cytoplasm [43].

11.2.2 Classification and Diagnosis

11.2.2.1 Classification

Clark et al. classified malignant melanoma into the following four subtypes by the clinical and histopathologic characteristics: superficial spreading melanoma (SSM), lentigo maligna melanoma (LMM), acral lentiginous melanoma (ALM), and nodular melanoma (NM) [13]. Characteristic histopathologic features of each subtype are detected in the growth component along the epidermis surrounding the invasive component into the dermis; the former component is called the radial growth phase (RGP) and the latter is the vertical growth phase (VGP). According to Clark et al., each subtype of melanoma is distinctive not only morphologically but also biologically [14]. They insisted that the VGP had potential for developing metastasis but there was no risk of developing metastasis in the RGP. The prognosis of NM developing as the VGP from the beginning was reported to be worst, LMM was least aggressive, and SSM and ALM were intermediate biologically. Later, however, it was reported that prognosis was not significantly different among Clark’s subtypes if stratified by tumor thickness [36]. Moreover, malignant melanomas showing ambiguous histopathologic features among the four subtypes are not rare. Ackerman criticized the validity of the Clark’s classification and proposed the unifying concept of malignant melanoma [2].

More recently, Bastian’s group proposed a new classification system of malignant melanoma [16]. Based on the anatomical sites and the degrees of sun-damages to skin, they classified malignant melanomas into the following four types: (1) melanomas occurring on skin without histopathologic signs of chronic sun-induced damage (non-CSD melanomas), (2) melanoma occurring on skin showing chronic sun-induced damage, which is histopathologically evidenced by definite solar elastosis (CSD melanomas), (3) melanomas occurring on acral skin hardly exposed to sunlight (soles, palms, and nail bed) (acral melanomas), and (4) melanomas occurring on mucosal membranes (mucosal melanomas). Non-CSD melanomas roughly correspond to SSM in Clark’s classification, CSD melanomas to lentigo maligna melanomas (LMM), and acral melanomas to ALM. Very importantly, the four types of melanomas defined by Bastian’s group exhibit distinct sets of genetic alterations, suggesting that this classification reflects essential differences in molecular pathogenesis. B-RAF (v-raf murine sarcoma viral oncogene homolog B1) or N-RAS (neuroblastoma v-ras oncogene homolog) mutations are very common in non-CSD melanomas, but mutation rates of these genes are low in the other three types. Moreover, acral melanoma is characterized by amplification of a variety of genes including cyclin
11.2 Malignant Melanoma

11.2.2 Clinical Diagnosis and Dermoscopy

11.2.2.1 Clinical Diagnosis and Criteria

The ABCDE rules and the Glasgow’s 7-point checklist are popular clinical guidelines for detection of malignant melanoma. The Glasgow’s checklist emphasizes the changes of lesions [38], whose sensitivity to early melanoma may be low. ABCDE rule is surely effective in differentiating early melanoma from acquired melanocytic nevus [1], but it may be not so effective in differentiating melanoma form basal cell carcinoma and seborrheic keratosis.

Most advanced melanomas are easy to diagnose clinically (Fig. 11.2.1a).

However, to improve prognosis, we must accurately diagnose this neoplasm in the earlier stages (Fig. 11.2.1b).

The following criteria may be helpful in the early detection.

1. Pigmented macule:
   - Variable shades of brown from tan to black
   - Disorderly and asymmetrical distribution of the colors

2. Irregular shape:
   - Asymmetrical overall configuration
   - Notching at the margin, often

3. Larger size:
   - Usually more than 7 mm in maximum diameter at the time of diagnosis (excluding congenital nevus, which is often larger than 7 mm)

4. Uneven margin:
   - Margin of the lesion abruptly stops partly and is indistinct in other parts.

Using the above criteria, we could effectively differentiate early melanoma from so-called Clark nevus (dysplastic nevus) [59].
11.2.2.2 Diagnosis with Dermoscopy

Dermoscopy (dermatoscopy, epiluminescence microscopy), a recently introduced non-invasive diagnostic method, is immensely helpful in determining diagnosis of malignant melanoma. Dermoscopy has revealed new valuable criteria for diagnosing malignant melanoma. The most systematic diagnostic procedure in dermoscopy is the two-step procedure proposed in Consensus Net Meeting on Dermoscopy held in 2000 [6]. Other several dermoscopic procedures have been proposed for the detection of malignant melanoma as follows: pattern analysis, ABCD rule [66], 7-point checklist [4], and Menzies’ method [42]. Among them, pattern analysis, first proposed by Pehamberger et al. [53] and later revised by Argenziano & Soyer et al. [5], may be most useful; diagnostic sensitivity was almost same among all the methods, but specificity in the revised pattern analysis was superior to other methods [6].

Melanocytic lesions on acral volar skin exhibit unique dermoscopic patterns. Major dermoscopic patterns seen in melanocytic nevus on acral volar skin are the parallel furrow pattern, the lattice-like pattern, and the fibrillar pattern [61, 62]. Among them, the parallel furrow pattern is the prototype (Fig. 11.2.2a) [61].

Other minor dermoscopic patterns of acral melanocytic nevus have been reported such as homogeneous pattern and reticular pattern [39]. In these benign dermoscopic patterns, pigmentation is prominent along the sulci of the surface skin markings, which run in a parallel fashion in this anatomical site. Interestingly, in macular portions of malignant melanoma affecting acral volar skin, the ridges of the skin markings are preferentially pigmented (Fig. 11.2.2b), which was referred to the parallel ridge pattern [51].

The parallel ridge pattern is frequently detected even in the earlier lesions of acral melanoma. In the stage of melanoma in situ, diagnostic sensitivity and specificity of the parallel ridge pattern are 86% and 99%, respectively [63]. Thus, acral melanoma can be effectively detected in the early curable stages by using dermoscopy.

11.2.2.3 Histopathologic and Genetic Diagnosis

Histopathologic differentiation between malignant melanoma and Spitz nevus is most challenging; Spitz nevus is not infrequently misdiagnosed as malignant melanoma and vice versa. Histopathologic criteria for the differentiation have been proposed [3], and typical cases can be correctly diagnosed by using these criteria. However, Spitz nevus-like lesions with some
atypical histopathologic features are not rare, which causes a serious problem in determining diagnosis. Some investigators recently proposed the concept of atypical Spitz nevus and of spitzoid melanoma [8, 11]. According to them, atypical Spitz nevus is a borderline lesion between Spitz nevus and melanoma and spitzoid melanoma is a biologically low-grade melanoma with limited potential of metastasis. Ackerman rejected such ambiguous entities and insisted that diagnosis must be melanoma or Spitz nevus [45]. Gill et al. reported that Spitz nevus and spitzoid melanoma were similar in genetic changes, both did not exhibit B-RAF mutations, which is common in ordinary malignant melanoma [26]. In contrast, van Dijk et al. reported that Spitz nevus and spitzoid melanoma were significantly different in mutation status of B-RAF, N-RAS, and H-RAS (Harvey rat sarcoma viral oncogene homolog) genes [69].

We analyzed a total of 16 spitzoid lesions showing ambiguous histopathologic features. We examined hot spots of mutation in the B-RAF, N-RAS, and H-RAS genes by PCR-based direct sequencing. In addition, we analyzed DNA copy number aberrations and the methylation in cancer-related genes by using methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) [68]. Two dermatopathologists independently interpreted a HE stained section of the cases. The two pathologists mostly agreed in the diagnosis of melanoma, however, most lesions diagnosed as Spitz nevus by one pathologist were interpreted as atypical Spitz nevus by the other. Cases diagnosed as melanoma exhibited mutations of B-RAF or N-RAS genes, and/or copy number aberrations of oncogenes or methylation of tumor suppressor genes. In contrast, in almost all cases diagnosed as Spitz nevus or atypical Spitz nevus, no genetic abnormalities were detected. These results indicate that atypical Spitz nevus is nothing but a kind of Spitz nevus.

11.2.3 General Therapeutic Outline

11.2.3.1 Staging and Prognosis

A new staging system of cutaneous melanoma was proposed by American Joint Committee on Cancer staging system in 2002. The TNM classification and the staging system are shown in Table 11.2.1. Key revised points are change of T classification criteria (from 0.75, 1.5 and 4 mm to 1, 2, and 4 mm) and introduction of category of microscopic metastasis in regional lymph nodes.

<table>
<thead>
<tr>
<th>pT classification (primary lesions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX: primary tumor cannot be assessed (e.g., shave biopsy or regressed melanoma)</td>
</tr>
<tr>
<td>T0: no evidence of primary tumor</td>
</tr>
<tr>
<td>Tis: melanoma in situ</td>
</tr>
<tr>
<td>T1a: tumor thickness ≤ 1 mm, without ulceration and level II/III</td>
</tr>
<tr>
<td>T1b: tumor thickness ≤ 1 mm, with ulceration or level IV/V</td>
</tr>
<tr>
<td>T2a: tumor thickness &gt; 1 mm, ≤ 2 mm, without ulceration</td>
</tr>
<tr>
<td>T2b: tumor thickness &gt; 1 mm, ≤ 2 mm, with ulceration</td>
</tr>
<tr>
<td>T3a: tumor thickness &gt; 2 mm, ≤ 4 mm, without ulceration</td>
</tr>
<tr>
<td>T3b: tumor thickness &gt; 2 mm, ≤ 4 mm, with ulceration</td>
</tr>
<tr>
<td>T4a: tumor thickness &gt; 4 mm, without ulceration</td>
</tr>
<tr>
<td>T4b: tumor thickness &gt; 4 mm, with ulceration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N classification (regional lymph nodes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX: regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0: no regional node metastasis</td>
</tr>
<tr>
<td>N1a: 1 node, micrometastasis (clinically occult)</td>
</tr>
<tr>
<td>N1b: 1 node, macrometastasis (clinically apparent)</td>
</tr>
<tr>
<td>N2a: 2–3 nodes, micrometastasis (clinically occult)</td>
</tr>
<tr>
<td>N2b: 2–3 nodes, macrometastasis (clinically apparent)</td>
</tr>
<tr>
<td>N2c: in transit metastasis/satellite(s) without metastatic nodes</td>
</tr>
<tr>
<td>N3: 4 or more metastatic nodes, or matted nodes, or in transit metastasis/satellite(s) with metastatic node(s)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M classification (distant metastases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX: distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0: no distant metastasis</td>
</tr>
<tr>
<td>M1a: distant skin, subcutaneous, or nodal metastases, normal serum LDH*</td>
</tr>
<tr>
<td>M1b: lung metastases, normal serum LDH</td>
</tr>
<tr>
<td>M1c: all other metastases, normal serum LDH or any distant metastasis, elevated serum LDH</td>
</tr>
</tbody>
</table>

*Lactic dehydrogenase
nodes, which is evaluated by the sentinel node biopsy. In addition, stage III is defined only as the stage with regional lymph node metastasis, irrespective of microscopic or macroscopic. Sub-stage categories are important in the new staging system. Based on data of 17,600 melanoma patients, 5- and 10-year survival rates of each sub-stage were presented [7], which surely aid in predicting survival of each patient. These survival rates were calculated from data of Caucasian melanoma patients. We investigated survivals of Japanese melanoma patients according to the new staging system (Table 11.2.1). Survival rates are mostly comparable between Balch’s series and ours, however, in sub-stages IIC and IIIB, survival rates of Japanese patients seem to be superior [50].

**11.2.3.2 Clinical Guidelines for Management of Cutaneous Melanoma**

In recent years, several clinical guidelines for management of cutaneous melanoma have been proposed from western countries: The National Comprehensive Cancer Network (NCCN) (http://www.nccn.org) and National Cancer Institute Physician Data Query (http://www.cancer.gov/cancer_information/pdq/) from U.S.A., Guidelines from the Government of Australia (http://www.nhmrc.gov.au/publications/subjects/cancer.htm), and Scottish Intercollegiate Guidelines Network (SIGN) (http://www.sign.ac.uk/). Almost all these guidelines are formulated based on the principle of the evidence-based medicine (EBM) [56]. These guidelines surely help physicians in the management of melanoma patients.

**11.2.4 Current Therapies and Management**

**11.2.4.1 Surgical Treatment of Primary Lesions**

Several randomized clinical trials have confirmed validity of narrow margin excision of primary melanoma [37]. Table 11.2.2 shows recommended excision margin in the several recent guidelines. Lesions of melanoma in situ are excised with 2–5 mm free margin, primary lesions up to 2 mm thickness are excised with about 1 cm free margin, and lesions more than 2 mm in thickness are excised with about 2 cm free margin.

**11.2.4.2 Sentinel Lymph Node Biopsy**

Introduction of sentinel lymph node biopsy has great impact on the management of regional lymph nodes [47]. The sentinel node(s) is the regional lymph node(s) first receiving the drainage from a particular anatomical site, which is identified with locally injected tracers such as blue dyes or radioisotope particles. If the sentinel node contains no microscopic metastasis, there is virtually no risk that the remaining regional lymph

### Table 11.2.1 (b) Stage grouping and 5-year survival of each sub-stage

<table>
<thead>
<tr>
<th>Stages</th>
<th>Definition of the stage</th>
<th>5-year survival rate&lt;sup&gt;a&lt;/sup&gt; Western</th>
<th>Japanese</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1aN0M0</td>
<td>95%</td>
<td>100%</td>
</tr>
<tr>
<td>IB</td>
<td>T1bN0M0, T2aN0M0</td>
<td>90</td>
<td>91</td>
</tr>
<tr>
<td>IIA</td>
<td>T2bN0M0, T3aN0M0</td>
<td>78</td>
<td>82</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3bN0M0, T4aN0M0</td>
<td>65</td>
<td>70</td>
</tr>
<tr>
<td>IIC</td>
<td>T4bN0M0</td>
<td>45</td>
<td>65</td>
</tr>
<tr>
<td>IIIA</td>
<td>T1a-4aN1a-2aM0</td>
<td>67</td>
<td>66</td>
</tr>
<tr>
<td>IIIB</td>
<td>T1a-4aN1b,2b,2cM0</td>
<td>53</td>
<td>62</td>
</tr>
<tr>
<td>IIIC</td>
<td>T1b-4bN1b,2bM0, anyTN3M0</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>IV</td>
<td>anyTanyNM1</td>
<td>12</td>
<td>13</td>
</tr>
</tbody>
</table>

<sup>a</sup>Cited from [7, 50]
nodes contain metastasis, and thus regional lymph node
dissection is not necessary. Cochran et al. proposed a
standardized histopathologic evaluation method of sen-
tinel node(s) \[15\]. Status of sentinel node has been con-
fi rmed as a significant prognostic factor, and a more
recent study suggested that sentinel node biopsy could
improve the prognosis of melanoma patients \[48\].

### 11.2.4.3 Adjuvant Therapy for High-Risk
Patients

Melanoma patients in the stages IIC or III are at high-
risk of recurrence after radical surgery. These patients
are candidates for adjuvant therapy. A randomized
controlled trial performed by Kirkwood et al. revealed
that long-term administration of high-dose interferon
alfa (IFN-α) (2000 × 10^4 unit/m^2/day, intravenously,
for 1 month and 1000 × 10^4 unit/m^2, three times per
week, subcutaneously, for 11 months) significantly
prolonged the survivals of high-risk melanoma patients
compared with the control group (overall 5-year sur-
vival: 46% vs 37, \( P = 0.02 \)) \[34\]. However, later studies
failed to confirm the significance \[35\]. At least at pres-
ent, no effective adjuvant therapies for high-risk mel-
anoma patients have been established.

### 11.2.4.4 Management of Metastatic
Lesions

If metastasis is solitary or only a few in number and
limited to one organ, feasibility of surgical resection is
considered. Surgical resection of such lesions may
prolong survival time of the patients to some extent
\[23\]. If metastasis is limited to the liver, intra-arterial
chemotherapy using cisplatin (CDDP) or other drugs
has some palliative effect on the patients’ quality of
life \[24\]. Hepatic arterial chemoembolization is also
considered in this situation \[41\].

Effect of chemotherapy on advanced melanoma with
multiple metastases is limited. DTIC is still a standard
drug for patients with metastatic melanoma. Treatment
schedule is (1) 200–250mg/m^2/day, intravenously (iv),
on day 1–5, or (2) 850–1,000mg/m^2/day, iv, on day 1
only, repeated every 3–4 weeks as far as tolerable. In
fact, however, the response rate by this drug is less than
20% and long term remission is exceptional. In a past
decade, new drugs such as fotemustine \[31\] and temo-
zolomide \[44\] were introduced, but their benefits were
limited, compared with DTIC. A variety of combination
chemotherapies were proposed. The Dartmouth regi-
men (BCDT) consisting of CDDP (25 mg/m^2, iv, on day
1–3, every 3–4 weeks), DTIC (220 mg/m^2, iv, on day
1–3, every 3–4 weeks), carmustine (BCNU) (150 mg/
m^2, iv, on day 1, every 6–8 weeks) and tamoxifen (TAM)
(20 mg/day, per os) was reported to show high response
rate around 50% in advanced melanoma \[19\], however,
later randomized controlled clinical trials failed to con-
firm superior effect compared with DTIC monotherapy
\[12\]. Another attractive regimen was sequential bio-
chemotherapy, in which combination chemotherapy
mainly using CDDP immediately followed by biother-
apy using interleukin-2 (IL-2) and IFN-α. Higher
response rate more than 50% and up to 20% complete
response was reported \[33\]. However, again, random-
ized controlled trials failed to confirm superior effect of
the sequential biochemotherapy compared with corre-
sponding combination chemotherapy alone \[57\]. Only
one study performed by Eton et al. showed borderline
significance in the survival (medium survival time: 9.3
months for chemotherapy alone versus 11.9 months for

<table>
<thead>
<tr>
<th>Tumor thickness</th>
<th>NCCN</th>
<th>UK</th>
<th>Scottish</th>
<th>NCI-PDQ</th>
<th>AAD</th>
<th>ESMO</th>
</tr>
</thead>
<tbody>
<tr>
<td>In situ</td>
<td>5 mm</td>
<td>2–5 mm</td>
<td>2–5 mm</td>
<td>5 mm</td>
<td>5 mm</td>
<td></td>
</tr>
<tr>
<td>≤1 mm</td>
<td>1 cm</td>
<td>1 cm</td>
<td>1 cm</td>
<td>1 cm</td>
<td>1 cm</td>
<td>1 cm</td>
</tr>
<tr>
<td>&gt;1 mm, ≤2 mm</td>
<td>1–2 cm</td>
<td>1–2 cm</td>
<td>1–2 cm</td>
<td>2 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2 mm, ≤4 mm</td>
<td>2 cm</td>
<td>2–3 cm</td>
<td>2 cm</td>
<td>2 cm</td>
<td>2 cm</td>
<td></td>
</tr>
<tr>
<td>&gt;4 mm</td>
<td>2 cm</td>
<td>2–3 cm</td>
<td>2 cm</td>
<td>2–3 cm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[NCCN: National Comprehensive Cancer Network
UK: Br J Dermatol 146:7, 2002; Scottish: Scottish Intercollegiate Guidelines Network; NCI-PDQ: National Cancer Institute/PDQ(melanoma); AAD: J Am Acad Dermatol 45:579, 2001; ESMO: European Society of Medical Oncology\]
biochemotherapy using IL-2 and IFN-α; \( P = 0.06 \) [21]. Note that these combination therapies increased incidence and severity of adverse effects.

Malignant melanoma is also highly resistant to radiation, however, radiation therapy can be used as a palliative therapy [54]. Stereotactic radiosurgery for cerebral metastatic melanoma is a choice of palliative treatment [46]. Pain from bone metastases can be transiently relieved by radiation therapy.

## 11.2.5 Experimental Approaches

### 11.2.5.1 Immunotherapy

Many melanoma antigens recognized by cytotoxic T cells (CTL) have been identified and amino acid sequences of peptides presented on HLA-molecules and recognized by T cell receptors were analyzed [55]. Among various kinds of immunotherapies, dendritic cell therapy seems to be most attractive. Dendritic cells derived from peripheral blood of patients are pulsed in vitro with a cocktail of melanoma epitope peptides or an autologous tumor lysate and then re-introduced to the patients. Disappearance of large visceral metastases was episodically reported, however, even in these patients, enlarging metastases or new metastatic lesions were often observed during the treatment [49]. This may be explained by loss of melanoma antigens and/or HLA-class I antigens from melanoma cells. Regulatory T cells also have an inhibitory effect on the functions of CTL. Clinical trials of humanized anti-CTLA-4 antibody, which reactivates CTL, have been conducted worldwide, particularly in combination with DTIC [28].

In a recent study by Rosenberg et al., autologous tumor infiltrating lymphocytes (TILs) were expanded in vitro and then transferred to HLA-A2+ patients, who had been received immunodepleting chemotherapy with cyclophosphamide and fludarabine. Along with the TILs, high-dose IL-2 was administrated to the patients. In this trial, 18 of 35 (51%) patients showed clinical response including three patients of complete response with duration 7–24 months [20]. Remarkably, in responded patients, CD8+ lymphocytes accounted for ~80% in the peripheral blood and percentages of the MART-1-reactive T cells were over 60–75% of CD8+ cells for up to 100 days. In this treatment, however, adverse effects were severe and EB virus-related lymphoma occurred in one patient.

### 11.2.5.2 Gene Therapy and Molecular Targeting Therapy

Various kinds of gene therapy have been tried for advanced melanoma [64]. However, significant clinical response was not obtained in any these trials. We tried gene therapy using expression plasmid of human IFN-β gene encapsulated in cationic liposomes. The liposomes were injected into the metastatic nodules of melanoma. Effects of this gene therapy were limited [40].

Recently, genetic alterations in melanoma cells have been precisely investigated and several activated or inactivated genes were found [10, 60]. The mitogen-activated protein kinase (MAPK) signaling cascade is activated in most melanoma cells [18, 67]. Clinical trials of molecular targeting therapy using small molecules blocking this pathway have started [25]. Bastian’s group recently found that oncogenic mutations in KIT gene were detected in acral and mucosal melanomas. The mutations and/or copy number increases of KIT gene were detected in 36% of acral melanomas [17]. They suggested imatinib methyate, a protein kinase inhibitor, could be useful in the treatment of acral melanoma with the KIT alterations, which was recently confirmed in a case of rectal melanoma [30].

### 11.2.6 Complications to Avoid

All the new treatment for patients with advanced melanoma must be carried out in a setting of the clinical trial. Possible severe adverse effect must be seriously considered before starting these trials.

---

**Take Home Message**

- Malignant melanoma is a curable disease if it is detected in the earlier stages. All physicians should have knowledge about characteristic clinical features of early melanoma.
- Advancement in basic immunology and in molecular biology will provide us with new diagnostic and therapeutic modalities for this lethal neoplasm in the near future.
11.2.7 Global Variations

Malignant melanoma shows big racial difference in the proportion of the subtypes as well as in the incidence. Ethnic variations in the melanoma subtypes may have important significance in the management.

In Japan, the DAVFeron therapy is now routinely used as an adjuvant therapy. It consists of combination chemotherapy composed of dacarbazine (DTIC), nimustine (ACNU), and vincristine (VCR) along with intracutaneous injection of IFN-β around the surgical scar of a primary lesion. Melanoma patients at stage III (UICC, 1997) showed significantly higher 5-year survival rate compared with historical controls [72]. However, evidence level of this study is rather low and the effect must be critically evaluated in a randomized trial.

Recently, an expert committee of Japanese investigators has published clinical guidelines for the management of malignant melanoma. In the guidelines, algorithm for management of cutaneous melanoma was also proposed (Fig. 11.2.3). The full guidelines are open on the web-site of the Japanese Dermatological...
Association (http://www.dermatol.or.jp/) and a simplified version of the guidelines is seen on the website of the Japan Society of Clinical Oncology (http://j sco.umin.ac.jp/index-3.html). Japanese physicians and patients with melanoma can get useful information from the guidelines.

References


11.3.1 Introduction

Cutaneous lymphomas (PCL) belong to the group of extranodal non-Hodgkin lymphomas; they are the second most common member of this group. Their incidence is estimated at 1/100,000, yearly. Primary CL develop, by definition, in the skin and must be confined to the skin at the end of staging, while secondary PCL reflect cutaneous spread from disseminated primary nodal lymphomas or leukemias. PCL represent clonal proliferations of neoplastic T or B lymphocytes, and rarely of NK cells or plasmacytoid dendritic cells. They have been recognized as a heterogeneous group with distinct variability in clinical presentation, histopathology, immunophenotyping, and prognosis.

Primary cutaneous lymphomas often show a completely different clinical behavior and prognosis compared to histologically similar systemic lymphomas, which may involve the skin secondarily. Therefore, primary cutaneous lymphomas require different types of treatment. For this reason, a new consensus classification based on both, the European Organization for Research and Treatment of Cancer (EORTC) classification for primary cutaneous lymphomas and the World Health Organization (WHO) classification for tumors of haematopoietic and lymphoid tissues as the first common classification, namely the WHO-EORTC classification, has been established [17]. The WHO-EORTC-classification categorizes the entities according to lineage and, subsequently, according to a combination of morphology, immunophenotype, genetic features, and clinical presentation and outcome (Table 11.3.1). In this chapter, we focus on the treatment of the most common cutaneous lymphomas, including the most frequent cutaneous T-cell lymphomas (CTCL): mycosis fungoides (MF), Sézary...
C. Assaf and W. Sterry

syndrome (SS), primary cutaneous anaplastic large cell lymphoma (cALCL), and lymphomatoid papulosis (LyP), and the most frequent cutaneous B-cell lymphomas (CBCL): primary cutaneous follicle center lymphoma (PCFCL), primary cutaneous marginal zone lymphoma (PCMZL) and primary cutaneous diffuse large B-cell lymphoma leg type (PCDLBCL). These seven types of cutaneous lymphomas represent more than 90% of all cutaneous lymphomas.

### 11.3.2 General Aspects

PCL are different from lymphomas of nodal origin in regard to clinical picture, course of disease, and therapy. As there is no curative therapy hitherto, treatment should be directed towards improvement of quality of life. Initial aggressive therapy, i.e., multiagent chemotherapy, will in most cases result in only a transient remission and is not able to improve overall survival [8]. Therefore an intense search for new therapeutically active agents, which are acting specifically on the tumor cells, is ongoing. Immune-therapies are of special interest as the tumor cells originate from B or T lymphocytes. For these cells a whole variety of surface antigens are well defined and monoclonal antibodies are available. In the following chapter, we describe current forms of treatment including standard protocols and recently described biological agents used in the treatment of PCL.

### 11.3.3 Treatment of Cutaneous T-Cell Lymphoma

Since CL is a heterogenous group of diseases, therapeutic strategies must reflect the exact diagnosis, previous treatment, and staging. There are few controlled studies containing all this information. In any case, the treatment of CTCL must be separated from that of CBCL. Mycosis fungoides (MF) as the most common and Sezary syndrome (SS) as a leukemic variant will be discussed in more detail. Another group of CTCL are the CD30+ lymphoproliferative disorders, nominally anaplastic large cell lymphoma and lymphomatoid papulosis, which are characterised by a relapsing course but an overall favourable prognosis. All other entities of CTCL are rare [17].
The clinical picture of MF is characterised by patches, plaques and tumors, which may occur separately as well as concomitantly. The latter may have a mushroom-like appearance being responsible for the term mycosis fungoides.

As there is no curative therapy hitherto the treatment of CTCL is stage-adapted. While therapy in early stages without extracutaneous involvement is skin directed, e.g., topical steroids, topical chemotherapy or phototherapy, in more widespread disease, combination of topical therapy with systemic agents as interferon-α and/or retinoids is advisable. Chemotherapy should be reserved for late stages of MF with visceral involvement as it results in selection of therapy-resistant tumor cell clones in most cases.

The Sézary Syndrome is a CTCL defined by erythroderma, leukemic phase and lymph node involvement at the time of diagnosis. Additional morphologic features are an often-intense pruritus and palmoplantar hyperkeratosis. In contrast to MF the prognosis for SS is much worse with a 5-year survival rate of only 24% [17].

Therapy with extracorporeal photopheresis (ECP) alone or in combination with interferon-α has been shown to induce complete remission. The ECP is a procedure during which leukocytes are separated from red blood cells, and are, after incubation with psoralen, radiated with UV light. An alternative first-line therapy is combination of PUVA and interferon-α. However, in advanced disease only single or multiagent chemotherapy may be able to, at least transiently stop disease progression. Because many treatment options and combinations for the different stages of these diseases exist, there are several paradigms and algorithms in the therapy for CTCL. One of the consensus recommendations of a stage adapted treatment schedule for MF and SS is shown in Table 11.3.2.

### 11.3.3.1 Patch/Plaque Disease

Cutaneous T-cells recirculate through the vascular system, capable of patrolling the entire skin. When CTCL lesions are scattered about the skin, the most successful treatment strategies are those that treat the entire skin so as to extend the antilymphoma effect to the entire realm of the cutaneous T cell. In isolated patch lesions or unilesional forms of mycosis fungoides class I–III (potent/moderate potency) topical corticosteroids can produce complete clinical remission (25–63%) but the duration of benefit may be short and prolonged use can cause cutaneous atrophy [19].

Therefore, the total skin treatment modalities most commonly used as first-line therapy against disseminated patch/plaque disease are phototherapies, topical chemotherapy, and total skin electron-beam radiotherapy.

<table>
<thead>
<tr>
<th>Clinical stages (MF)</th>
<th>First-line treatment</th>
<th>Second-line treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIA–IIA</td>
<td>PUVA</td>
<td>Oral bexarotene INF-α monotherapy INF-α retinoids</td>
</tr>
<tr>
<td></td>
<td>UVB (patches only)</td>
<td>Denileukin diftitox</td>
</tr>
<tr>
<td></td>
<td>Topical corticosteroids</td>
<td>Low-dose MTX</td>
</tr>
<tr>
<td></td>
<td>Localized radiotherapy</td>
<td>INF-α + PUVA Retinoids + PUVA Bexarotene + PUVA</td>
</tr>
<tr>
<td></td>
<td>TSEB (≤3 treatments)</td>
<td>Carmustine Nitrogen mustard</td>
</tr>
<tr>
<td>IIIB</td>
<td>PUVA + INF-α</td>
<td>Oral bexarotene Denileukin diftitox</td>
</tr>
<tr>
<td></td>
<td>TSEB, superficial X-irradiation</td>
<td>Chemotherapy HDACI</td>
</tr>
<tr>
<td></td>
<td>Retinoids + INF-α</td>
<td>Carmustine Nitrogen mustard</td>
</tr>
<tr>
<td></td>
<td>PUVA + retinoids</td>
<td>ECP PUVA + retinoids</td>
</tr>
<tr>
<td>III</td>
<td>PUVA + IFN-α</td>
<td>Oral bexarotene INF-α</td>
</tr>
<tr>
<td></td>
<td>IFN-α monotherapy</td>
<td>HDACI</td>
</tr>
<tr>
<td></td>
<td>MTX</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td></td>
<td>TSEB/ X-irradiation</td>
<td>Carmustine or nitrogen mustard</td>
</tr>
<tr>
<td></td>
<td>Carmustine or nitrogen mustard ECP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PUVA + retinoids</td>
<td>(\times 3) treatments</td>
</tr>
<tr>
<td>IV A–IVB</td>
<td>Chemotherapy</td>
<td>HDACI</td>
</tr>
<tr>
<td></td>
<td>TSEB and/or X-irradiation</td>
<td>Oral bexarotene INF-α</td>
</tr>
<tr>
<td></td>
<td>Oral bexarotene</td>
<td>Denileukin diftitox</td>
</tr>
<tr>
<td></td>
<td>Denileukin diftitox</td>
<td>IFN-α</td>
</tr>
<tr>
<td>SS</td>
<td>ECP</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td></td>
<td>INF-α</td>
<td>Alemtuzumab</td>
</tr>
<tr>
<td></td>
<td>Denileukin diftitox</td>
<td>Chlorambucil/ prednisone</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy</td>
<td>MTX</td>
</tr>
<tr>
<td></td>
<td>Chlorambucil/ prednisone</td>
<td>Oral bexarotene INF-α</td>
</tr>
</tbody>
</table>

---

### Table 11.3.2 Recommendations for first- and second-line treatments of MF and SS
11.3.3.1.1 Phototherapies

Administration of oral 8-methoxypsoralen (8-MOP) and UVA radiation can produce a definite clinical response and complete remissions of long duration in patients with patch/plaque CTCL. PUVA therapy requires regular treatments, initially three to four times a week for up to 3 months or until remission occurs. The follow-up of a patient on PUVA for CTCL includes an assessment to be sure there is some mild degree of phototoxicity. Otherwise, there may be insufficient dosing of either the psoralen or the UVA light. Risks of the treatment include possible induction of cutaneous epithelial neoplasms and cataract formation. Therefore, all patients should be observed closely and checked regularly for development of skin cancer. In addition, patients are advised to protect their eyes for 24 h following PUVA therapy. These precautions should be enforced early because PUVA is a therapy that may continue for years as a maintenance treatment. Even after poor responses with conventional therapy, patients have had complete clearing of the skin with PUVA [15]. However, maintenance therapy may be needed, as shown by the prolongation of clinical remission with continued PUVA.

UVB and narrow band ultraviolet B (NBUVB) are both effective for CTCL. These phototherapies are more convenient for patients although their efficacy, especially for plaque disease, may not be as great as PUVA. Patch CTCL can often be completely cleared with UVB or NBUVB [16]. A complete response can typically be induced with three to five treatment sessions per week. After a complete response has occurred, phototherapy can be continued on a maintenance schedule initially at once per week. The acute toxicities are primarily due to phototoxicity and the chronic toxicity is the increased risk for cutaneous malignancy.

11.3.3.1.2 Total-Skin Topical Chemotherapy

This consists of nitrogen mustard (mechlorethamine hydrochloride) that is applied as either an ointment base or as a freshly prepared aqueous solution. As an initial dose, 10 mg of the drug is dissolved in approximately 50 mL of tap water. The entire volume is then applied to the whole body surface by the patient. The patient should wear protective plastic gloves while applying the solution. A delayed hypersensitivity reaction may complicate treatment and it is possible to desensitize patients, although their confidence in the therapy may be compromised. Ointment-based mechloretamine, typically 10 mg% in ointment, may be less sensitizing and is stable on the shelf over a long period of time. Other side effects from mechlorethamine hydrochloride therapy, besides hypersensitivity reactions and primary irritant reactions, include the development of second cutaneous malignancies and hypo- and hyperpigmentation. This method is relatively easy for the patient to use at home, but daily whole-body application is required with maintenance therapy once remission is induced [20].

11.3.3.1.3 Total-Skin Radiation Therapy

The radiosensitivity of cutaneous lymphomas has been therapeutically exploited by total-skin electron-beam (TSEB) radiation. Because electrons penetrate only to the upper dermis, electron-beam therapy may be used without systemic effect. The limited penetration of the electrons is advantageous in that it spares the mucous membranes, bone marrow, gastrointestinal tract, and other vital internal organs. Only those portions of the skin that are directly exposed to the beam are radiated. Therefore, palms, soles, scalp, axillae, and perineum may need separate exposure to ensure total-body treatment. The eyelids are routinely covered with lead eye shields to protect the cornea and lens from the effects of radiation.

Whole-body electron-beam irradiation brings about complete remission in 80–95% of patients. The relapse rate is highest in the later stages of CTCL, that is, in those patients with tumors, lymphadenopathy, and visceral involvement. Patients with limited plaque disease had the best relapse-free rate (42% at 10 years). Most relapses occurred within the first year after completion of therapy and were very rare after 3 years. The median disease-free interval was greater than 3 years in the limited plaque group, approximately 1 year for patients with generalized plaque or erythrodermic disease, and less than 6 months for patients with cutaneous tumors. The total dose of irradiation is important, and a dose of 30 cGy (3,000 rad) or more gives better complete remission rates and disease-free survival than do lower ones. The major disadvantages are that this type of therapy requires a specialized center, and takes up to 3 months for complete treatment.
Topical side effects include alopecia, atrophy of sweat glands and skin generally, radiodermatitis, and edema. When the total dose is highly fractionated, these complications are minimized and often avoided. The question is what is the maximum radiation tolerance of the skin? With the highly fractionated approach, patients can receive a second course of electron beam therapy of 36 cGy (3,600 rad) to reinduce a remission. As the total radiation dose increases, so does the risk of squamous cell carcinoma and radiodermatitis. Small-field or spot orthovoltage radiotherapy using soft x-rays (60–100 kV with half-value layers of 1–1.5 mm Al) fractionated to doses of 0.75–5 cGy (75–500 rad) and total doses of 8–15 cGy (800–1,500 rad) will adequately eliminate most lesions [7].

11.3.3.2 Erythroderma

The erythrodermas of CTCL represents a total-skin redness, scaling, and severe pruritus. It is not surprising that immune-based therapies take the forefront in the management of these disorders. The three major biologic response modifiers (BRMs) used in the treatment of CTCL are oral retinoids, intravenous extracorporeal photochemotherapy (ECP), and subcutaneous injections of interferon-α. In the clinical trials of these agents, patients have undergone monotherapy of what has usually been heavily pretreated refractory disease. In practice, these are often used first line as monotherapy in erythroderma and combination therapies are incorporated if there is an incomplete response. With these agents, partial responses are more common than complete responses. Thus, if the goal is remission, a combination therapy is more common than monotherapy. If the goal is palliation, monotherapies with BRMs are often sufficient. The BRMs differ in terms of their administration, side effects, interactions with other therapy modalities, and their availability.

11.3.3.2.1 Retinoid Therapy

The first-generation retinoids such as isotretinoin have an impact on CTCL. The more CTCL-specific retinoid, bexarotene, selectively binds the retinoid X receptor, whereas the other available retinoids have less-specific binding patterns. In the monotherapy trials, bexarotene was dosed at 300 mg/m² (average dose, 450–675 mg day⁻¹, taken as capsules with the evening meal). Responses were seen at all phases of the disease: plaques, erythroderma, and tumors. Responses paralleled the secondary endpoints: decreases in overall body surface area involvement, overall tumor aggregate area, and improvement in pruritus. Erythrodermic patients may experience increased desquamation during the first few weeks of oral bexarotene therapy. Improvement typically occurs by week 12 of therapy [4].

Although there appeared to be a dose–response relationship with respect to efficacy, the higher doses were also associated with a higher rate of adverse events and dose-limited toxicities. The most common were hyperlipidemia/hypercholesterolemia and neutropenia. Elevations in the lipids occurred rapidly, within 2–4 weeks. Institution of monitoring lipids and use of lipid-lowering drugs were helpful in controlling the lipid levels. Dose reductions of bexarotene capsules were also required in some patients. Drug interactions of oral bexarotene with gemfibrozil and warfarin have been observed.

Patients started on bexarotene develop central hypothyroidism with low thyroid-stimulating hormone (TSH) and free thyroxine levels within weeks of starting the medication. Symptoms of hypothyroidism may be subtle because they include symptoms of fatigue and feeling cold that may be attributed to CTCL. Supplementation with levothyroxine while patients were on bexarotene alleviates the symptoms and improves tolerance to treatment. The mentioned adverse events are all reversible and manageable with the use of concomitant medication [1]. There is no immunosuppression with bexarotene therapy. Patients on bexarotene typically have monthly monitoring visits to follow lipid, liver, and thyroid parameters.

11.3.3.2.2 Extracorporeal Photopheresis

Extracorporeal photopheresis (ECP) is as well a widely accepted type of photochemotherapy used for the treatment of CTCL, especially in patients with erythroderma (Stage III) or SS. ECP therapy involves the photoinactivation of a portion of a patient’s lymphocyte compartment with 8-methoxypsoralen (8-MOP) in the presence of ultraviolet A light, followed by reinfusion of these
cells. The treatment is performed via an intravenous line feeding into a photoinactivation device that typically requires the patient to be recumbent for 3 h. Treatments are conducted on 2 consecutive days every 4 weeks. Improvement may begin as early as 6 weeks into therapy, and yet some patients do not completely clear until 12 months after starting therapy. There were occasional temporary responses immediately following a 2-day cycle of therapy. On average, after 4–6 months there was typically a gradual and permanent decrease in erythema, scaling, and pruritus. Patients often notice more subtle changes such as the return of body hair, loss of rigors, and a return of the ability to sweat. Partial responses may also decrease the morbidity these patients suffer in terms of infectious complications. More heavily involved and inflamed skin is more readily colonized, providing both a reservoir and access point for microbes to invade the host. Thus, cutaneous improvement can also minimize complications of CTCL.

11.3.3.2 α-Interferon

Interferon alpha has been shown in a number of studies to be a highly active agent in CTCL with an overall response rate ranging from 40% to 80% [12]. α-Interferon is typically started at 3 million units (MU) three times a week and can be increased to a maximally tolerated dose, typically in the range of 12 MU day⁻¹. Like the other BRMs, the response to interferon is gradual, with 3–6 months being needed to determine the maximal response. After patients achieve a maximal response, interferon can be lowered to a maintenance dose of 1 MU daily.

Constitutional symptoms and bone marrow suppression have limited aggressive and long term use of interferons for many patients. The initial week of interferon is complicated by a flu-like illness that may be accompanied by fever, myalgia, fatigue, and listlessness. As this wears off, patients are often left with a slight feeling of chronic fatigue. The long-term toxicity that causes most concern is neurologic: depression, neuropathy, dementia, and myelopathy. There are autoimmune phenomena that may occur such as proteinuria, thrombocytopenia, and anemia. Monitoring of interferon therapy includes blood counts and urinalysis along with questionnaires assessing the impact on the quality of life.

The combined modality therapies that use interferon in the management of erythrodermas include ECP and retinoids. If monotherapy of erythroderma produces a partial response, the addition of either of these agents can induce the desired goals of either complete response or increased palliation.

11.3.3.3 Cytotoxic Chemotherapy

A number of agents have demonstrated activity in CTCL. These include alkylating therapies, such as cyclophosphamide, chlorambucil doxorubicine, gemcitabine and methotrexate [3, 10, 18]. While combination chemotherapy regimens have produced higher responses in patients with advanced refractory CTCL, these responses have not been durable. Because of the high risk of infection and myelosuppression and modest response durations with combination chemotherapy, single-agent therapies are preferred except in patients who are refractory or who present with extensive adenopathy and/or visceral involvement and require immediate palliation [8].

11.3.3.4 Novel Approved Treatment Modalities for CTCL

While life-expectancy for patients with limited skin involvement is excellent and closely comparable to a healthy population (Stages Ia and Ib 5-year survival rates are 100% and 96%, respectively) the 5-year survival rate for patients with lymph node involvement drops to 40% in cases of MF and it is only 30% in patients with SS. With the involvement of any other organ prognosis is getting even worse and the 5-year survival rate is 0% with a median survival of 13 months. Because conventional treatments result only in a transient remission without curative results in most cases, there is high need for new therapeutic strategies with acceptable side effects. Recently biological drugs have been developed which already passed through clinical trials and broaden the therapeutic options in the treatment of patients with relapsing or recalcitrant CTCL.

11.3.3.4.1 DAB 389 IL-2

(Synonyms: Denileukin Diftitox, Ontak®) is a recombinant cytotoxic fusion protein composed of the
receptor-binding domain of the human interleukin-2 (IL-2) molecule and a mutated diphtheria toxin (DT) molecule.

The target structure of DAB<sub>389</sub> IL-2 is the IL-2-receptor (IL-2R), which is expressed on activated lymphocytes and monocytes as well as CTCL cells. The complex of DAB<sub>389</sub> IL-2 bound to the IL-2R is internalized by endocytosis. After proteolytic cleavage of the fusion protein the DT fragment becomes active and binds to the elongation factor-2. Thereby protein synthesis is inhibited resulting in cell death by apoptosis.

DAB<sub>389</sub> IL-2 is administered intravenously in two different dosages (9–18 ug/kg bodyweight) once daily on 5 consecutive days every 3 weeks for up to eight cycles. In immunohistochemical studies a high level of CD25 expression (equal or more than 20% of lesional T cells) was significantly associated with clinical response. In a phase III trial 144 CTCL patients were treated. The overall clinical response rate was 49%, with 10% showing a complete remission. The median duration of remission lasted for 6.9 months (range from 2.7 to 46.1 months). The quality of life and pruritus as assessed by questionnaires improved significantly in responders compared to non-responders [11, 13].

Infusion related adverse events were hypotension, chest or back pain and dyspnea. Also flu-like symptoms like fever, chills and nausea occurred. Only few patients suffered from severe adverse events like allergic reactions or a capillary-leak syndrome. Transient elevation of liver enzymes and hypoalbuminemia were observed in serum analysis. Premedication with paracetamol, antihistamines or in severe cases systemic steroids may increase tolerability of DAB<sub>389</sub> IL-2 infusions. Taken these data together DAB<sub>389</sub> IL-2 is a generally well-tolerated additional treatment option in patients with CTCL refractory to standard therapy regimens [2].

11.3.3.4.2 Alemtuzumab

(Campath-1H, MabCAMPATH<sup>®</sup>) is a humanized monoclonal IgG antibody binding to CD52. The CD52 antigen is expressed on monocytes, granulocytes, B and T lymphocytes and clonally proliferating malignant lymphocytes. CD52 is not expressed on hematopoietic stem cells. Alemtuzumab has to be administered three times weekly at a dosage of 30 mg for a maximum of 12 weeks. All patients receive premedication with paracetamol and antihistamines. As infectious prophylaxis cotrimoxazole and acyclovir has to be given throughout the treatment. Achieved overall response rates in different studies are about 30–50%, showing that erythrodermic patients responding better compared to plaque or tumor stage patients. A strong reduction of pruritus was observed in responding patients. The median time to relapse was 12 months, ranging from 5 to 32 months [9].

Side effects in temporal association to the infusion were generally mild reactions like fever, nausea or allergic reactions and could be controlled with premedication. However, infectious complications (30%) are frequent and sometimes fatal, including severe pulmonary aspergillosis Mycobacterium pneumonia. Reactivation of cytomegalovirus was detected in 18% of patients, presenting as fever without pneumonitis. All of these patients could be successfully treated with intravenous ganciclovir. Another potential complication of alemtuzumab is cardiac toxicity reported in up to 50% of patients. Therefore, alemtuzumab should be considered as an option in patients with advanced MF/SS disease who did not respond to previous systemic therapies. Because of the potential severe infectious complications patients should receive antibiotic and antiviral prophylaxis and have to be monitored closely for early signs of infections.

11.3.3.4.3 Histone Deacetylase Inhibitors

The acetylation status of histones is involved in regulation of gene transcription. While histone acetylation favors DNA transcription, histone deacetylases keep the DNA in a transcriptional inactive state. Histone deacetylase inhibitors (HDACIs) increase the acetylation status of histones and thereby facilitate the transcription of genes involved in cell differentiation, cell cycle arrest and apoptosis.

Currently several substances, namely vorinostat, romidepsin, panobinostat and belinostat from the group of HDACIs are investigated for the treatment of CTCL. Of these vorinostat has been approved as the first HDACI for the treatment of refractory CTCL. An open label phase IIb multicenter study has been performed by Olsen et al [14], evaluating the efficacy and tolerability of vorinostat in 74 progressive and relapsing patients with MF including 30 patients with SS who had at least
two prior systemic therapies. Patients received 400 mg vorinostat orally per day. The overall response rate was 29.7% of all patients and in 36.4% of patients with SS. The median time to response was 56 days and the overall median time to progression was 148 days for all patients.Observed adverse events were fatigue, symptoms, nausea, dry mouth, and decreased appetite. Thrombocytopenia (grade 3 or 4) occurred in 18% of patients. In conclusion HDACIs showed clinical activity in CTCL patients, who were refractory to previous therapy. Therefore vorinostat may serve as an alternative therapy in patients with refractory or progressive CTCL.

11.3.4 Treatment of Primary Cutaneous B Cell Lymphoma

The cutaneous B cell lymphoma (CBCL) comprise around 25% of all cutaneous lymphomas. The three most common subtypes are the marginal zone lymphoma (MZL), the follicle center cell lymphoma (FCL) and the diffuse large B cell lymphoma (DLBCL), leg type. Albeit a high tendency to relapse MZL and FCL have a very good prognosis with a 5-year survival rate of 99% and 95%, respectively. The DLBCL, leg type tends to grow more aggressively and the 5-year survival rate is only 55%.

Primary CBCL without other features have a much better prognosis than the corresponding nodal B-cell lymphoma, even when they are histologically classified as “highly malignant.” In many cases topical therapy is sufficient. Excision is one option; another is radiation therapy (soft X-rays 6–10 x 2 Gy; 30–50 kV, twice weekly electron beam 40 Gy). In some instances IFN therapy can lead to complete remission. Systemic polychemotherapy is only indicated with extracutaneous manifestations. While standard therapy for the indolent CBCL is excision or radiation the diffuse large B cell lymphoma, leg type often requires chemotherapy, e.g., in combination with the monoclonal antibody rituximab (R-CHOP).

11.3.4.1 Rituximab

Rituximab (MabThera®) is a recombinant chimeric IgG antibody binding to the human CD20 antigen. CD20 is expressed on pre-B cells and mature B-lymphocytes, expressed on >90% of B-cells in non-Hodgkin lymphoma. CD20 expression is not detectable on haematopoietic stem cells, plasma cells, or non-haematopoietic tissues. The effect of rituximab is mediated by induction of apoptosis in target cells, antibody-dependent cellular cytotoxicity and complement-mediated cytotoxicity. In the treatment of CBCL rituximab has been used as systemic infusion as well as intralesional injection.

An applicational observation reported on ten patients with CBCL (PCFCL, PCMZL) receiving rituximab i.v. with a dosage was 375 mg m⁻² body surface area once per week, up to 8 weeks. All patients received premedication with hydroxyhydrochloride and indometacin. Complete remission was observed in 7/10, while 2/10 patients had a partial remission. The mean duration of remission was 23 months. Observed side effects were infusion-related fever, shivering and nausea. Laboratory analysis showed a nearly complete depletion of B cells leaving other parameters, e.g., creatinine and alkaline phosphatase unchanged. During the study two patients suffered from bacterial infections, albeit no severe adverse events were recorded.

Intralesional administration of rituximab has also been shown to be effective in the treatment of CBCL. In a retrospective study patients received 10 mg rituximab intralesional in up to four lesions three times weekly. Cycles were repeated every 4 weeks for up to eight cycles. With this regimen a complete remission was observed in 6/7 patients. While in one patient the tumor recurred topically after 27 months, two patients had recurrence at distant body sites after 12 and 14 months, respectively. Side effects were burning sensations at the injection site during and several hours after injections. Interestingly, B cells were depleted from the circulation indicating systemic effects of topically applied rituximab. Intralesional injection of rituximab is especially suitable for solitary or few lesions as systemic adverse events were not observed and the amount of rituximab is less than for systemic application thus lowering treatment costs. Currently rituximab is recommended as second-line treatment for patients with relapsing or refractory CBCL and is generally well tolerated.

References

11.4 Etiology and Pathogenesis

Vascular malformations are a heterogeneous group of disorders that should be differentiated from the more common infantile hemangioma for which they may be mistaken. The updated biologic or Mulliken classification provides the framework for classifying vascular birthmarks and divides vascular birthmarks into two broad categories, vascular tumors, which includes the common infantile hemangioma, and vascular malformations, which are classified according to their vessel type and flow characteristics (Tables 11.4.1 and 11.4.2). Vascular malformations may be composed of capillaries, veins, arteries or lymphatics or a combination of these vessels. Each of the most common type will be briefly discussed in this section [27].

Cutaneous vascular malformations are rare disorders representing errors in vascular development that occur in less than 1% of the population [68]. The majority of vascular malformations arise sporadically but in rare cases familial forms are described. Vascular malformations are believed to be errors in vascular development; however, their pathogenesis is not clearly understood. Recent developments in molecular genetics have provided clues to the pathogenesis of some rare familial forms of these disorders and likely prove to be essential in understanding the pathogenesis of the more common sporadic forms.

11.4.1 Capillary Malformations

Capillary malformations (CM) are slow-flow lesions composed of small post capillary venule sized vessels. They occur in approximately 3 of 1,000 infants and are often called port wine stains. [49, 68]. In this chapter, the term port wine stain will be used interchangeably with capillary malformation to describe these lesions. A subset of capillary malformations occur more commonly in infants and have been given a variety of names including “vascular stains,” “angel’s kiss,” “salmon patch,” “stork bite,” “nevus simplex,” and “fading macular stains” to distinguish them from port wine stain type CMs and to emphasize their benign prognosis. It is estimated that these birthmarks, which are frequently located in on the central face (glabella, eyelids, nose, upper lip) and the nape of the neck occur
in 30–50% of newborns and fade without treatment in the first 2 years [74]. Vascular stains on the neck may persist into adulthood but rarely require any treatment because of their location. Vascular stains located on the eyelid may be difficult to distinguish from true port wine stain CMs or an early infantile hemangioma that has not yet begun to proliferate significantly, therefore reassessment of the birthmark as the infant matures may be essential to establish the correct diagnosis.

Biopsy specimens of CMs reveal an increased number and ectasia of blood vessels in the dermis. The majority of the vessels of a CM are located in the papillary and reticular dermis with the number of anomalous vessels decreasing with increasing depth. There is variability in the vessel depth that is dependent on the location of the lesion. Some studies have suggested that lesions in the V2 dermatome and distal extremities have more deeply placed vessels while the V3 dermatome, neck, and trunk region tend to be more superficial [29]. The mean vessel area and fullness percent increase with age while the vessel number and depth correlates poorly with age. The former finding explains the change in color of the lesion from pink to violet as the individual matures. Video microscopy of CMs has revealed three different patterns of vascular ectasia. The described patterns are ectasia of the vertical loops of the papillary plexus, ectasia of the deeper horizontal vessels in the papillary plexus, and a mixed pattern [5, 6, 35]. These different patterns may account for the variability in response to pulsed dye laser treatment.

Immunohistochemical analysis has demonstrated a decreased number of neurons associated with the vasculature in port-wine stains [85]. It is speculated that an alteration in the neural modulation of vascular flow may be involved in the pathogenesis of CMs [81, 84, 85]. However, the reduced density of neuronal cells may not be involved in the pathogenesis and may be secondary to abnormal vasculature and relative ischemia.

While several proteins and receptors integral to vasculogenesis and angiogenesis have been proposed to cause vascular malformations, only a few have been linked to CMs specifically. A relatively recently recognized autosomal dominant disorder CM-AVM syndrome is characterized by capillary malformations occurring in association with cutaneous and cerebral arteriovenous malformations (AVM). Genetic mapping has identified RASA1, encoding p120-rasGTPase activating protein (p120-rasGAP), as the causative defect. p120-rasGAP appears to be integral to signaling for various growth factor receptors that control proliferation, migration and survival of several cell types,
including vascular endothelial cells [22]. Investigators have also speculated that another protein, developmental endothelial locus-1 (Del-1) may play a role in some cases of CM. Del-1 is an extracellular matrix protein adhered to by human umbilical vein endothelial cells, which has been shown to induce formation of a vascular plexus with a high number of small capillaries [47]. Despite these recent findings, the molecular pathogenesis has yet to be elucidated for the majority of patients with CMs.

### 11.4.1.2 Venous Malformations

Venous malformations (VMs) are slow-flow vascular malformations that are present at birth. They are composed of anomalous dilated venous channels. A variety of terms including “venous angioma,” and “cavernous hemangioma,” have been used to describe these malformations in the medical literature. These terms have led to confusion with the more common proliferating infantile hemangioma and should be abandoned. VMs are relatively rare congenital anomalies. These lesions usually arise sporadically, but familial VMs can occur and are inherited in an autosomal dominant manner. A distinct subset of venous malformations, glomuvenous malformations (previously called glomangiomas or venous malformations with glomus cells in the literature) has recently been characterized and shows features that are distinct from typical mucocutaneous venous malformations [7].

The histopathology of typical venous malformations reveals poorly circumscribed lesions composed of irregular, endothelial-lined vascular channels. The lumen walls are thin and deficient in smooth muscle cells [67]. The molecular basis of sporadic VMs has not been elucidated however; there have been recent advances in the understanding of familial cases. Vikkula and colleagues found that an activating mutation in the gene for the endothelial cell receptor Tie2 was associated with mucocutaneous venous malformations in several families [92]. Earlier studies suggested that Tie2 signaling plays a significant role in the branching and sprouting of the capillary plexus [83]. The mutation seen in these families with inherited VMs resulted in increased activity of the receptor tyrosine kinase. It has been proposed that increased activity of this receptor tyrosine kinase leads to abnormal sprouting and branching, which results in VMs. Additional research has identified ligands for the Tie2 receptor, angiopoietin-1 and angiopoietin-2. These proteins are believed to play a role in regulating the assembly of non-endothelial components of the vessel including smooth muscle [17, 36, 65, 86]. Moreover, Fachinger et al. suggested that a vascular endothelial-protein-tyrosine phosphatase (VE-PTP), which is more strongly expressed in vessels invested with smooth muscles than in capillaries and small veins, protects arteries and large veins from increased Tie2 activity, thereby resulting only in malformed cutaneous venules/veins [30]. Not all familial cases of VMs are associated with this mutation, which suggests that venous malformations are genetically heterogeneous [13].

Glomuvenous malformations (GVM) are less common than typical venous malformations representing approximately 5% of venous anomalies, and are inherited in an autosomal dominant pattern in 64% of cases [7]. Mutations in the gene *glomulin* located on chromosome 1p21-22, cause glomuvenous malformations [10]. Studies suggest that glomus cells within glomuvenous malformations represent abnormally differentiated vascular smooth-muscle cells. Therefore, it is suggested that glomulin plays a role in the differentiation of vascular smooth muscle cells [66].

### 11.4.1.3 Lymphatic Malformations

Lymphatic malformations (LMs) are slow-flow developmental anomalies of the lymphatic system that result in abnormalities in lymphatic flow. Lymphedema is a term to describe a diffuse lymphatic anomaly. It may be primary or secondary (acquired). Acquired or secondary lymphedema is the most common lymphatic anomaly and is usually secondary to localized damage to the lymphatic vessels following, infection, trauma or surgery. Primary lymphedema is relatively rare and can occur in isolation or in association with other developmental abnormalities such as in Noonan and Turner syndromes [60]. Primary lymphedema can be divided by age of presentation into congenital familial type I (Nonne-Milroy disease), type II lymphedema praecox (late-onset hereditary lymphedema, or Meige disease), and lymphedema tarda [12, 54]. Milroy disease is usually inherited in an autosomal dominant manner, and
often presents at birth with lymphedema of the lower extremities. Lymphedema praecox typically presents during adolescence with lymphedema of one or both legs. Lymphedema tarda is defined as primary lymphedema presenting after 35 years of age. Hennekam syndrome is a very rare autosomal recessive disorder consisting of congenital lymphedema, intestinal lymphangiectasia and mental retardation [90].

Congenital lymphatic malformations are frequently referred to as “lymphangiomas,” and can be divided into microcystic, macrocystic or combined lesions. Microcystic LMs are called lymphangioma circumscriptum and macrocystic LMs are sometimes referred to as cystic hygromas. The distinction between macrocystic and microcystic LMs is important due to its relevance in treatment and prognosis. These two types may also be combined or associated with other vascular malformations.

The pathogenesis of LMs is not clearly understood. Early theories proposed that “lymphangiomas” and “cystic hygromas” are sequestrations of lymphatic tissue with inherent growth capacity, which fail to communicate with the venous system [82]. Others proposed that LMs represented benign neoplasms of the skin and subcutaneous tissue [97, 99]. In the current biological classification these lesions are categorized as malformations rather than true tumors that show hyperproliferation [11].

In the early stages of lymphangiogenesis, lymphatic vessels are part of the vascular bed. Endothelial cells express proteins LYVE-1 and VEGFR-3 and later, there is variable expression of the homeobox gene Prox-1 by these cells. Chang et al. noted that in mouse cornea, bFGF triggered lymphangiogenesis at levels lower than those needed to induce angiogenesis, suggesting this growth factor’s involvement in signaling [14]. Cells that express LYVE-1, VEGFR-3, and Prox-1 are then committed to lymphatic lineage and begin to secrete secondary lymphoid chemokine (SLC) and increase expression of VEGFR-3. Subsequently maturation of the lymphatic system ensues, with the presumed involvement of members of the angiopoietin family and their receptors. The protein tyrosine kinase Syk and its substrate SLP-76, which may participate in signaling of lymphatic vessel growth away from the rest of the vascular system may also play a role in the development of lymphatics [1, 50].

Owing to these findings, there are several candidate genes that may be responsible for LMs. VEGFR-3 and its ligands VEGF-C and VEGF-D are involved in lymphangiogenesis. It has been shown that transgenic mice with over-expression of VEGF-C develop selective lymphatic hyperplasia [51]. In addition, studies of families with autosomal dominantly inherited Milroy’s disease have demonstrated a mutation in the gene expressing VEGFR-3 on chromosome 5q [33, 34]. There is also speculation that homeobox gene Prox-1 could be involved in the pathogenesis of LMs [96]. In addition, mutations of the FOXc2 gene on chromosome locus 16q24.3, which encodes for forkhead proteins involved in multiple developmental processes, are found in the rare form of lymphedema that is associated with distichiasis (double row of eyelashes) [32]. These findings provide us with clues to the development of LMs, but their pathogenesis remains poorly understood.

11.4.1.4 Arteriovenous Malformations

Arteriovenous malformations (AVMs) are fast-flow vascular lesions composed of abnormal arterial and venous vessels connected directly to one another without an intervening capillary bed. The pathogenesis of AVMs is not well understood. It is likely that their development is related to mutations in genes that encode for proteins that are essential for normal vascular development. It is speculated that they arise during early fetal development, secondary to the failure of regression of arteriovenous channels in the primitive retiform plexus. This theory would explain the predominance of AVMs in the head and neck region, since cephalic structures predominate in the early embryo and the cheeks and ears, common facial sites of AVMs, have higher surface area to volume ratio than other facial structures during early embryonic development [55]. Although most cases of AVMs are sporadic, there are few inherited syndromes whose molecular genetics have been recently elucidated. The rare condition CM-AVM syndrome is associated with a mutation in gene RASA1, expressing p120-rasGAP, on chromosome 5q [22]. AVMs are also seen in the autosomal dominant condition, hereditary hemorrhagic telangiectasia (HHT).

Analysis of abnormal vasculature in HHT reveals direct arteriolar to venular connections and loss of normal intervening capillary segments [37, 44]. HHT is genetically heterogeneous and mutations in at least
three genes have been described in families with the disorder. Two types are better characterized than the more recently described third subtype HHT 3. The first and more common form maps to a locus on chromosome 9q33-34 which is the site of the ENG gene which encodes for endoglin, a transforming growth factor β binding protein. A second locus is on chromosome 12q11-14 which is the site of the ALK1 gene whose product is an activin-like tyrosine kinase-1 [52, 63]. Both of these genes encode an integral membrane glycoprotein expressed mainly on vascular endothelial cells as the surface receptor for the TGFβ superfamily, which mediates vascular remodeling through effects on extracellular matrix production [37]. There is speculation that, like HHT, sporadic AVMs may be associated with an abnormality in the TGF-β signaling pathway [93]. There is evidence that TGF-β is involved in the induction of apoptotic endothelial cell death [8]. There is also research to support the idea that a reduced apoptotic process may cause the dysregulation of vascular growth in AVMs [95]. Further understanding of inherited syndromes may also clarify the pathogenesis of sporadic lesions. In addition, it is proposed that a defect in ephrins or their receptors may be a causative factor in the formation of AVMs. Differences in expression of Ephrin-B2 and its receptor Eph-B4 distinguish arterial endothelial cells from venous endothelial cells in early embryogenesis, Abnormalities in this expression pattern results in defects in vessel development which has led investigators to conclude that the reciprocal signaling between these two types of vessels is critical in the formation of capillary beds [39, 94].

Mutations in the Notch signaling pathway may also play a role in the development of AVMs. This pathway plays an essential role in vascular development in vertebrates. Abnormalities in the pathway were reported to result in abnormal development of the arteriovenous system in zebrafish embryos. Moreover, mouse embryos that demonstrate mutations in genes involved in this pathway are noted to have AVMs [56, 59]. Further investigation is needed to determine whether these signaling proteins may be implicated in the development of AVMs in humans. Although the cause of AVM expansion is unknown, it has been proposed that their expansion/progression to more active stages, may result from dormant primal arteriovenous communications, dilation of normal, latent arteriovenous shunts by increased pressure and flow, and local ischemia caused by trauma [18].

11.4.2 Clinical Characteristics and Diagnosis

11.4.2.1 Capillary Malformations

Capillary malformations are usually noted at birth, but may initially be misdiagnosed as a bruise or erythema from birth trauma. Port wine stain type CMs are differentiated from the more common fading vascular stains (salmon patches) by their location and appearance. The term port wine stain will be used as a synonym for CM in this section. The appearance of CMs varies considerably but in young infants often are red patches that may initially lighten in the first few weeks, which may be due to a physiologic reduction of the hemoglobin levels in the first few weeks of life (Fig. 11.4.1)

However, they subsequently darken with maturity and in some cases develop blebs and become hyperkeratotic. CMs present as small patches or may involve an entire limb or portion of the face they may be single or multiple lesions. Involvement of the head and neck is common. Lesion involving the central and lower face may extend onto mucosal surfaces and ultimately be associated with soft tissue hypertrophy of these areas. The development of blebs and hyperkeratotic areas within CMs on the extremities is typically seen.

Fig. 11.4.1 Capillary malformation (port wine stain) of the face and scalp in a neonate
in association with lymphatic and/or venous malformation. Limb capillary malformation may also be associated with congenital hypertrophy of underlying bone and soft tissues. They may demonstrate a patchy or geographic pattern on the surface of the skin. Patchy lesions show less clearly defined borders while geographic capillary malformations demonstrate well-defined borders and are often associated with underlying lymphatic anomalies and progressive limb hypertrophy [61].

CMs of the skin may occur in association with other congenital malformations, including underlying vascular anomalies or other structural abnormalities of ectodermal origin, such as bony or soft tissue hyperplasia or atrophy, or neurologic defects (Table 11.4.3). The two most commonly recognized syndromes are Klippel–Trenaunay syndrome (KTS) and Sturge-Weber syndrome (SWS). Klippel–Trenaunay syndrome is characterized by a CM on an extremity (lower limbs are more commonly affected than upper limbs) variable soft tissue and bony hypertrophy of the limb and venous varicosities/venous anomalies. Lymphatic malformation may also occur along with the venous anomaly. The less common Servelle-Martorell is characterized by CM and venous malformation of a limb and limb undergrowth.

Sturge-Weber Syndrome is characterized by a facial dermal capillary malformation (port wine stain), ipsilateral CNS vascular malformation (leptomeningeal vascular malformation) and vascular malformation of the choroid of the eye associated with glaucoma. The CM is typically located on the upper face involving the eyelids. The majority of cases are associated with CMs affecting the skin innervated by the first branch of the trigeminal nerve, Some individuals with SWS appear to have V2 PWS alone, this disparity in findings may be attributed to a difference in definition of the distribution of the V1 and V2 areas, which is probably due to anatomic variability in the so-called “watershed area” of the upper and lower eyelids which can be enervated by either V1 or V2. The overall incidence of ocular or CNS involvement in patients with capillary malformations located in the V1 and V2 areas is reported to be approximately 8% but is considerably higher when multiple dermatomes (V1, 2, 3) or bilateral stains are present [87].

Other anomalies have been associated with CMs including underlying spinal dysraphism which may

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Vascular malformation</th>
<th>Associated features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sturge–Weber</td>
<td>Facial CM</td>
<td>Leptomeningeal vascular malformation (seizures)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ocular vascular malformation (glaucoma)</td>
</tr>
<tr>
<td>Klippel–Trenaunay</td>
<td>CVM limb (lower &gt; upper) or CLVM</td>
<td>Soft tissue and bony overgrowth of the ipsilateral limb</td>
</tr>
<tr>
<td>Parkes–Weber</td>
<td>CAVM, CLAVM limb</td>
<td>Limb hypertrophy</td>
</tr>
<tr>
<td>Servelle–Martorell</td>
<td>CVM limb</td>
<td>Limb undergrowth</td>
</tr>
<tr>
<td>Proteus</td>
<td>CM, LM, CLVM</td>
<td>Hemi hypertrophy, lipoma, epidermal nevi</td>
</tr>
<tr>
<td>Bean (blue rubber bleb nevus)</td>
<td>VM</td>
<td>Gastrointestinal VMs, bleeding, CNS vascular malformations</td>
</tr>
<tr>
<td>Maffucci</td>
<td>VM or spindle cell hemangioma</td>
<td>Enchondromas</td>
</tr>
<tr>
<td>Wyburn mason (Bonnet Duchame Blanc)</td>
<td>AVM central face</td>
<td>CNS AVM</td>
</tr>
<tr>
<td>Cobb</td>
<td>AVM paraspinal skin</td>
<td>Spinal AVM</td>
</tr>
<tr>
<td>Hereditary hemorrhagic telangiectasia (Osler–Weber–Rendu)</td>
<td>Telangiectasia</td>
<td>CNS, pulmonary, gastrointestinal AVMs</td>
</tr>
<tr>
<td>C – Capillary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L – Lymphatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V – Venous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A – Arterial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M – Malformation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Vascular Malformations occur not only in the classic lumbar location, but also in the cervical area when the stain is associated with an underlying mass or pit [16, 24]. A retrospective review has suggested that the combination of two or more midline cutaneous lesions is highly suggestive of occult spinal dysraphism in children [43]. The decision to perform an evaluation for spinal dysraphism when isolated capillary malformations occur in the lumbosacral area remains controversial and clear guidelines regarding the need for screening spinal evaluations are lacking.

**11.4.3.2 Venous Malformations**

Venous malformations VMs are present at birth but are not always evident. They become more prominent with maturity. They usually present as soft, compressible blue masses that enlarge when the affected area is in a dependent position or with physical activity (Fig. 11.4.2)

The blue color is caused by the presence of dilated anomalous venous channels within the dermis. There is no increase in local skin temperature or thrill when the lesion is palpated. These lesions arise at all sites and may be localized or more extensive. Facial VMs involve the skin and subcutaneous layers, but may extend into the muscle and oral mucosa. As VMs enlarge, the adjacent or underlying bone may be deformed. VMs located in the head and neck area and mucosal surfaces may cause significant cosmetic defects, lead to recurrent bleeding, obstruct the airway, and interfere with normal speech and dentition.

VMs on the extremities may be localized or segmental but extensive involvement is less common. Pure VMs of the extremities (to be distinguished from lesions seen in KTS) may extend into the skeletal muscles and joints and may be associated with either diminished girth or slight hypertrophy of the affected limb. This is in contrast to patients with Klippel–Trenaunay syndrome who experience progressive limb overgrowth. Deep VMs that lack superficial skin involvement and may remain unrecognized until a patient presents with pain, swelling or functional impairment later in life. Pain is a common complaint in extremity VMs. Pathologic fractures may also occur. Spontaneous local venous thrombosis may result in the formation of calcifications (phleboliths) within the VM. Localized intravascular coagulation within a VM may result in abnormal coagulation profiles and lead to episodes of thrombosis and/or bleeding. VM-associated bleeding diathesis usually develops in adolescence or early adulthood. It is to be differentiated from Kasabach–Merritt syndrome, which occurs in infants with vascular tumors (Kaposiform hemangioendotheliomas and tufted angiomas) [25, 26].

Glomuvenous malformations may present at birth or become more apparent with maturity, GVMs present as blue-purple nodules and papules with a “pebbly” surface (Fig. 11.4.3).

They may be isolated small lesions or larger plaques involving segments of the skin surface. They usually are more firm and less compressible than typical
venous malformations and may be painful with prolonged compression. They are less likely to extend into deeper subcutaneous structures such as the muscle and joints compared to typical venous malformations.

11.4.2.3 Lymphatic Malformations

Many LMs present at birth, with the remainder presenting by 2 years of age [76]. Many large studies show no sex predilection while others report a higher incidence in males [9, 46, 69, 82]. Macrocystic LMs are usually visible at birth and may be diagnosed by prenatal ultrasound. The majority of macrocystic LMs are located on the neck or axilla, where they are often called “cystic hygroma.” They are poorly circumscribed subcutaneous masses that expand over time, as the anomalous channels become dilated. They may be asymptomatic, or associated with local pain or tenderness.

Complications of macrocystic LMs depend upon their size and location. Cervicofacial LMs may impede vaginal delivery and also cause airway obstruction and difficulty with feeding and speech development. Complications of cervicofacial LMs include potentially life-threatening infections, and skeletal hypertrophy. Orbital LMs have the potential to cause ocular swelling, pain, congenital cataract, acute proptosis, strabismus or diplopia [41, 46].

Microcystic LMs are present at birth, but may not become apparent until later in life. Infection and bleeding may develop over time and makes the lesions more prominent. Microcystic LMs frequently present as groups of hyperkeratotic papules or vesicles on the surface of the skin (Fig. 11.4.4)

Closer inspection of the background skin may reveal swelling. They can be located anywhere on the skin surface. The term “lymphangioma circumscriptum” has been used to describe this presentation however, this term is a misnomer because these lesions are rarely circumscribed and often deeper dermal and subcutaneous anomalies [73]. Complications include ulceration, bleeding, and secondary infection. In addition, squamous cell carcinoma may arise within a long-standing congenital microcystic LMs [98]. LMs may also be a component of complex combined vascular malformations, such as in Klippel–Trenaunay syndrome.

11.4.2.4 Arteriovenous Malformations

AVMs occur with equal frequency in males and females. Approximately 50% are visible at birth and 30% become clinically apparent during childhood. They are more common in the head and neck area than other locations. The appearance of the AVM will depend upon its stage. The Schobinger clinical staging system describes four stages [28, 55] In Stage I lesions are in the quiescent phase, are asymptomatic, and the AVM may be unapparent or have the appearance of a CM or a resolving infantile hemangioma. The presence of increased warmth, a bruit or thrill suggests a high flow component. This stage often lasts from birth to adolescence. Some AVMs remain quiescent throughout a patient’s lifetime. During Stage II, the progressive phase, the AVM darkens and invades deep structures. Local skin temperature is increased, a pulse or thrill can be palpated, and a murmur is heard on auscultation and dilated draining vessels become more apparent. Progression to this stage is associated with puberty, trauma, and pregnancy. In addition, some forms of treatment, such as partial excision, ligation of arterial feeders, incomplete arterial embolization, can trigger progression of quiescent AVMs [55]. Stage III usually develops after years of worsening and, grossly mimics stage II, but deep destruction occurs with spontaneous necrosis, chronic ulceration, pain, hemorrhage. Finally Stage IV is characterized by cardiac decompensation. High output cardiac failure may result from increased blood flow in large AVMs.
11.4.3 General Therapeutic Outline

Prior to embarking on the treatment of vascular malformations it is essential to establish the correct diagnosis and recognize potential extracutaneous associations. The specific management of the lesion will depend upon the lesion type (vascular components and flow characteristics), location of the vascular malformation, age of the patient, and the potential for disfigurement or functional impairment. It is important to recognize and discuss with patients when a treatment modality will result in cure as opposed to palliation of symptoms. A multidisciplinary approach is required for the management of the majority of vascular malformations and many institutions have Multidisciplinary Vascular Anomalies Clinics to facilitate the care of individuals with vascular malformations.

11.4.4 Current Established Therapies of Capillary Malformations

Capillary malformations are diagnosed based upon their clinical appearance. It is important to note that cutaneous erythema overlying a deeper arteriovenous malformation may mimic a CM. This should be suspected if there is an associated increase in warmth on the surface of the lesion, a thrill on palpation or a history of pain. Doppler ultrasound evaluation is useful but not always diagnostic in suspected cases to detect an arteriovenous fistula or shunt. Once the diagnosis of CM is established, the patient should be carefully examined for the presence of underlying venous or lymphatic malformations and associated congenital anomalies. Individuals with suspected SWS or KT syndrome should be carefully evaluated (Table 11.4.4). Studies such as MR, Doppler scans, and even arteriography may be necessary in a minority of cases to evaluate for an underlying or associated anomaly. Currently MR evaluation with contrast enhancement is the preferred imaging technique to evaluate for the leptomeningeal vascular malformation associated with SWS.

The flash lamp pumped pulsed dye laser (PDL) is the treatment of choice for port wine stain/capillary malformations. Pulsed dye laser treatment of these lesions is based on the principle of selective photothermolysis. The pulsed dye lasers are designed to specifically target the chromophore, oxyhemoglobin, within the skin tissue which results in intravascular coagulation and selective destruction of the vasculature while minimizing injury to other skin structures [3, 88]. The lasers used most commonly employ wavelengths that selectively target oxyhemoglobin (577, 585, 595 nm). The selected pulse duration (often 450 μs or 1.5 ms) limits destruction and heat dissipation to the targeted vasculature without causing damage to the surrounding structures in the epidermis or dermis. Second generation PDLs employ longer wavelengths, higher fluences, longer pulse widths, and use of dynamic cooling devices the latter of which allows the higher fluences to be employed while reducing the risk of epidermal damage.

Complete disappearance of a port wine stain is unusual; however cosmetically acceptable lightening occurs in the majority of those treated [38, 40]. Reyes and colleagues reported that 80% of PDL treated port wine stain type CMs demonstrate good results with significant lightening [80]. Another study of 118 port-wine
stains treated with PDL demonstrated 50–90% lightening in 65% of treated lesions. Only 15% of the treated port-wine stains demonstrated greater than 90% lightening. The remainder of the lesions responded poorly or were unresponsive to therapy [72]. Multiple treatments often 6–8 weeks apart are required in the majority of individuals. Adverse reactions to pulsed dye laser treatment are uncommon but include, pigment alteration, and atrophic or hypertrophic scarring [5, 88].

Response to therapy and the number of treatments required to achieve lightening varies and may depend on the location, color, thickness and age of the port-wine stain. Centrofacial and limb lesions respond less well than other facial locations [79]. Younger patients respond better with more significant lightening, and require fewer treatments than older patients. Controversy exists regarding the optimal timing of treatment of young children with PWS. Some studies report dramatic response to early treatment (in the first several months of life) while another study found no evidence that treatment of port-wine stains with PDL in early childhood is more effective than treatment later in the first decade of life [2, 4, 91]. Frieden has hypothesized that some of the lightening that occurs in the first few months of life in PWS that have either been treated or untreated may be attributed to the physiologic decrease in hemoglobin levels that occurs in infants in the first few months of life (Frieden IJ, personal communication, June 2006). Younger patients, particularly those with larger lesions, may require general anesthesia to treat extensive port-wine stains and it is usually well tolerated [42]. Despite controversy regarding when in childhood laser therapy is more effective, treatment during early childhood is desirable to reduce the psychological impact of a cosmetically significant congenital malformation [57, 62]. Although treatment is successful in the majority of younger individuals there remain lesions that fail to respond to PDL therapy [53]. In addition, effects from PDL therapy may plateau after 6–10 treatments, resulting in residual lesions that may not meet patient satisfaction. Some patients who have undergone successful treatment using the traditional PDL may demonstrate re-darkening of their lesions years after completion of treatment [48, 72]. Individuals undergoing treatments should be counseled about this possibility of recurrence. “Touch-up” treatments may be useful for some patients who experience recurrences.

Over the last several years newer pulsed dye lasers that allow the user to employ longer wavelengths (595 nm) and pulse widths and higher fluences have been used to treat “resistant” CMs. A recent study suggests that variable-pulse 595-nm PDL may be effective in treating resistant larger diameter and deeper lesions and 532-nm Nd:YAG laser may be effective in treating resistant superficial lesions [101]. Multiple pass treatment, involving the use of two PDL passes for each laser session has also been reported for resistant CMs [5, 19]. In addition, other laser and light therapy options include longer wavelength lasers in millisecond modes such as the Alexandrite (755 nm) and Nd:YAG (1,064 nm). Potassium titanyl phosphate laser has also been shown to produce further lightening in PDL resistant port-wine stains. There may be an increased risk of side effects such as atrophic scarring in these laser therapies [15]. Intense pulsed light (IPL) such as the Photoderm VL demonstrates a lower overall response rate than PDL for most PWS however it may have a role in treatment of PDL-resistant port-wine stains [58, 77]. These studies seem promising however more studies will need to be performed to determine the risk of scarring associated with treating children with these newer technologies.

11.4.5 Current Established Therapies of Venous and Lymphatic Malformations

Evaluation and treatment of cutaneous venous, lymphatic, arterial and mixed malformations is best performed by a multidisciplinary team approach. Involvement of specialists in dermatology, plastic surgery, pediatric and general surgery, hematology, otorhinolaryngology, ophthalmology, genetics, and interventional radiology is both practical and facilitates treatment.

The general goals of therapy are to prevent disfigurement, preserve function, limit bony deformation, and minimize painful swelling. Prior to intervention, a coagulation profile should be obtained to rule out an underlying coagulopathy in individuals with VMs as it would require management prior to treatment. VMs are usually treated with surgical excision, sclerotherapy, or a combination of both. Surgical excision alone may not be possible for widespread lesions, but it may be an option for smaller, less extensive lesions. Surgery may also be employed to manage VMs that involve the
joints. Moreover sclerotherapy alone may be an option for smaller lesions. Smaller VMs involving the skin and muscle may improve with partial treatment with sclerotherapy. Patients may report reduced swelling and discomfort but the treatment is rarely curative.

The management of VMs depends upon the location of the lesion. Head and neck VMs and trunk or limb VMs are often approached differently. Typically large head and neck VMs are treated with a combined approach of often image guided percutaneous sclerotherapy performed by an interventional radiologist followed by surgical excision. Treatment of large lesions on the head and neck is often started in childhood to prevent disfigurement. Large trunk and limb VMs are difficult to manage because they may extend into muscles and joints, patients are usually managed conservatively. Patients with larger lesions have a high incidence of chronic localized intravascular coagulation (88%) and a mildly decreased platelet count [25]. The use of custom fitted compression garments starting in childhood is important in the management of limb lesions. Compression helps to decrease the discomfort associated with the lesion, protects the overlying skin, limits swelling, and improves localized intravascular coagulation. Prior to starting compression it is important to assure that the deep venous system is intact. Doppler ultrasonography is useful for this evaluation.

Glomuvenous malformations are often managed similarly to typical VMs however they may respond differently to treatment than typical venous malformations. Small, localized lesions can be managed with surgical excision however; sclerotherapy may be less effective and compression may cause discomfort in some individuals [7, 66].

Lymphatic malformations represent a treatment challenge. Management of large lesions includes maintaining vital functions particularly of large macrocystic head and neck LMs. Immediate management may require establishing an airway, or needle decompression of the mass. Bacterial superinfection can complicate LMs and is potentially life-threatening. Enlargement of the mass may be an early sign of this complication. Suspected infections should be treated promptly with appropriate antibiotics. Symptomatic LMs are most commonly managed with surgical excision. Surgical success is more readily attained in cases that are localized and well demarcated, and can be completely excised in one step. However, multiple procedures may be required and complete excision may not be possible in because of the risk of functional compromise. Recurrence rates vary with reports ranging between 0% and 27% for total excisions and (53–100%) for partially excised lesions [9, 31, 46]. Continuous-wave and ultrapulse carbon dioxide lasers, and Neodymium-YAG laser have employed to treat LMs with variable degrees of success. In many cases these lasers are used to reduce the drainage of from the superficial component of the symptomatic microcystic LM. Recurrences may occur following laser this treatment [45, 89].

Interventional radiologists play an important role in the management of cutaneous vascular malformations. Percutaneous methods to treat cutaneous vascular malformations have existed in many forms for over 100 years. Augmented by recent technological developments used for minimally-invasive surgery, interventional radiologists are accustomed to using many forms of image-guidance for assessment and percutaneous treatment of many vascular, infectious, and neoplastic diseases. When a patient is referred for image-guided therapy (sclerotherapy or embolization which is employed to treat AVMs), there has usually been some prior evaluation including physical examination and non-invasive imaging. Careful corroboration of the history, physical examination and laboratory studies must be performed. Computed tomography without or with iodinated contrast may provide specific information about size, distribution, vascular supply, and some soft tissue characteristics, such as calcifications that may be useful in diagnosis. However, magnetic resonance (MR) imaging is most helpful in confirming the diagnosis of a VM and LM and delineating the extent of involvement [76]. Moreover it does not require ionizing radiation, and usually provides better tissue resolution for all components except calcification. Ultrasound with color Doppler is also useful for evaluation of vascular malformations, although ultrasound not infrequently renders false information about vascularity, particularly high-flow arterial components. Schlobinger Stage I and II arteriovenous malformations may be difficult to identify by physical examination. If arteriovenous malformation or fistula is a diagnostic consideration, then catheter arteriography prior to implementation of any treatment plan is warranted.

While the pathogenesis, diagnosis, and clinical management of lymphatic and venous malformations are separate and clinically distinct, the approach to percutaneous sclerotherapy treatment of these two
types of vascular malformations has many similarities. Historically, percutaneous sclerotherapy was performed to palliate surgically unresectable LMs. More recently, image-guided sclerotherapy has become an accepted alternative to surgical resection in many cases. It is unlikely that sclerotherapy cures these lesions in the same manner as total surgical resection; however, functional palliation through volume reduction and cicatrization is frequently accomplished with a lower risk of iatrogenic morbidity. Table 11.4.5 lists a number of agents that have been used to treat lymphatic and venous malformations. These sclerosing agents are more effective in treating VMs and macrocystic LMs than microcystic LMs [21, 64, 70, 71, 75, 100]. Some of these agents such as bleomycin have specific potential toxicities associated with their use and a full review of this topic is outside the scope of this chapter. Ethanol is a highly effective sclerosing agent treatment that is often used to treat venous malformations. Its use is associated with a lower risk of recurrences than other agents put treatment is painful and is performed with the patient under general anesthesia. Other potential complications of percutaneous sclerotherapy include necrosis of the overlying skin post-inflammatory pigment alteration and infection [20]. Ethanol toxicity and cardiovascular events are rare complications of this therapy. Parents should be counseled to expect exaggerated soft tissue swelling due to sclerotherapy. For lesions that may impact any component of the child’s airway, preconsultation with the attending anesthesiologist is mandatory. Multiple treatments followed by surgical reconstruction may be required for acceptable treatment of a larger VM.

For both pediatric and adult patients with prior cross-sectional imaging studies, ultrasound guidance is usually adequate to obtain percutaneous needle access to the macrocystic components of both lymphatic and venous malformations. For injection therapy alone, a 25–27 gauge needle is adequate. Percutaneous drainage of macrocystic lymphatic malformations is performed prior to sclerotherapy. Reduction in lymphatic fluid volume helps maintain high concentrations for low volume sclerosant administration. For venous malformations, initiation of the coagulation cascade within the malformation creates substantial intraluminal thrombosis and inflammation. During injection, the sclerosing agent is opacified with a radio-opaque contrast material. Brief periods (1–2 s) of low dose and well columnated fluoroscopy are used to assure intra-lesional administration of the active agent without vascular or extra-lesional extravasation.

To prevent extravasation of a liquid sclerosing agent out of the malformation along the catheter tract, the tract can be sealed using one of a number of tissue adhesives. A bandage is applied to the access site(s). Intravenous antibiotics may be helpful to prevent bacterial seeding. Anti-inflammatory agents such as NSAIDs and glucocorticoids should be reserved to modulate the inflammation due to sclerotherapy. Patients with peripheral lesions are monitored for several hours in a post-anesthesia care unit for evidence of tissue necrosis, vascular compromise, or anesthetic or other drug reaction. Lesions with potential airway compromise may require prolonged endotracheal intubation and intensive care. Coordination of the care plan with all consulting physicians is both desirable and reassuring to the family.

11.4.6 Current Established Therapies of Arteriovenous Malformations

Treatment techniques will start with a discussion of arteriovenous malformations (AVM) because AVM is sometimes in the differential diagnosis even prior
to treatment of other types of vascular malformations. Catheter arteriography is often used to confirm the diagnosis of AVM and plan its treatment. Alternatively, arteriography may rule out AVM prior to endovascular or percutaneous treatment of another type of vascular lesion. The angiographic hallmark of AVM is arteriovenous shunting, rapid passage of iodinated vascular contrast from artery to vein either through a vascular nidus or isolated fistula. AVMs may overlap conventional boundaries between different vascular territories which has been useful to classify head and neck lesions, in particular. A detailed working knowledge of vascular anatomy and embolization techniques is necessary to minimize risk of transcatheter embolization and occlusion of AVMs. Moreover, these procedures are performed using ionizing radiation, exposure to which must be kept as low as reasonably achievable (ALARA). Consequently, interventional neuroradiologists often perform these catheter procedures even for treatment of peripheral AVMs because of their primary experience treating the comparatively more common brain AVMs.

Endovascular occlusion of AVMs should be performed in the context of an overall surgical plan. The goal of AVM embolization may be partial occlusion to facilitate surgical resection or for palliation of an unresectable lesion. Palliative embolization reduces tissue hydrostatic pressure, surgical blood loss, surgical morbidity and mortality. There is some evidence that partial endovascular occlusion of the nidus, or core of the AVM, without subsequent resection may ultimately lead to recurrences through collateral vessels that are more difficult to manage than the original lesion. Most AVMs are potentially amenable to complete endovascular occlusion although the risk of surrounding, normal tissue damage may out-weigh any potential benefit of the embolization. Training, judgment, and experience are necessary to limit serious complications.

There are numerous agents with variable physical and chemical properties that are useful for embolization procedures. A number of embolic materials are currently in use and many more are under development or employed in clinical practice outside the United States. Table 11.4.6 represents a listing and some characteristics of some of the more commonly used embolic materials. A complete review of the specific applications of these embolic agents is beyond the scope of this text.

### Table 11.4.6 Agents for endovascular embolization

<table>
<thead>
<tr>
<th>Agent</th>
<th>Physical state</th>
<th>Manufacturer</th>
<th>Application</th>
<th>Permanence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyvinyl alcohol</td>
<td>Particulate</td>
<td>JNJ, BSCI</td>
<td>Pre-operative tumor, AVM embolization</td>
<td>++</td>
</tr>
<tr>
<td>Gelfoam sponge</td>
<td>Pledget (hand cut)</td>
<td>Upjohn</td>
<td>Traumatic hemorrhage</td>
<td>+</td>
</tr>
<tr>
<td>Gelfoam powder</td>
<td>Particulate</td>
<td>Upjohn</td>
<td>Pre-operative tumor, AVM embolization</td>
<td>++</td>
</tr>
<tr>
<td>Avitene</td>
<td>Particulate</td>
<td>Medchem</td>
<td>Pre-operative tumor, AVM embolization</td>
<td>+</td>
</tr>
<tr>
<td>Platinum coils</td>
<td>Metallic coil</td>
<td>Cook, BSCI</td>
<td>Tumor, AVM</td>
<td>++++</td>
</tr>
<tr>
<td>Detachable platinum coils</td>
<td>Metallic coil</td>
<td>BSCI; JNJ: Cook; MTI; Terumo: Micrus</td>
<td>Aneurysm, AVM</td>
<td>++++</td>
</tr>
<tr>
<td>Balloons</td>
<td>Latex</td>
<td>Balt</td>
<td>Fistula</td>
<td>+++</td>
</tr>
<tr>
<td>Ethylene vinyl alcohol</td>
<td>Precipitate</td>
<td>Ev3</td>
<td>AVM</td>
<td>+++</td>
</tr>
<tr>
<td>Cyanoacrylate</td>
<td>Liquid adhesive</td>
<td>JNJ</td>
<td>AVM, Fistula</td>
<td>++++</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Sclerosant</td>
<td>Abbott</td>
<td>Fistula, AVM</td>
<td>++++</td>
</tr>
<tr>
<td>Ethanolamine oleate</td>
<td>Sclerosant</td>
<td>Questcor</td>
<td>Hemangioma, venous, and lymphatic malformations</td>
<td>++++</td>
</tr>
</tbody>
</table>
Take Home Message

› Vascular malformations are a heterogeneous group of disorders. Prior to embarking on treatment it is essential that the correct diagnosis is established. Clinical characteristics are helpful for establishing the diagnosis but supporting studies are often required. Radiographic procedures such as Doppler ultrasonography, MR imaging and even arteriography may be required. Moreover the association of vascular malformations with other developmental must be recognized. Individuals with lesions with the potential for systemic involvement must be identified an appropriately evaluated. A multidisciplinary approach is often essential for the care of individuals with vascular malformations

References

11.5.1 Introduction

This chapter covers a series of highly divergent malignancies from topically aggressive with frequent recurrences, only rare metastases, and a good long term survival to highly aggressive, rapidly metastatic lesions with short term survival. Lesions have in common to be rare, are many times clinically misdiagnosed, often with delay, and have characteristic clinicopathologic correlations, including immunophenotypic and molecular genetic findings. Besides karyotyping from tissue cultures, more recently fluorescence in situ hybridization (FISH) and reverse transcriptase polymerase chain reaction (RT-PCR) have been particularly helpful in detecting specific translocations, gain and loss of chromosomal material or fusion genes and their products. Most recently, further developments of designed drugs interacting with fusion genes and/or products such as imatinib (Glivec®) have opened up a fascinating new therapeutic field with dramatic impact and effects on tumor growth and regression. Besides cutaneous sarcomas, this chapter also covers another rare and aggressive, clinically often misdiagnosed entity, Merkel cell carcinoma.

Sarcomas are malignant mesenchymal neoplasias, which usually arise in deep soft tissue, less commonly in the subcutis, and rarely primarily in the dermis. The most common cutaneous entities in order of decreasing frequency are dermatofibrosarcoma protuberans, leiomyosarcoma, liposarcoma, Angiosarcoma, Malignant Peripheral Nerve Sheath Tumor, etc.

Key Features

- “cutaneous soft tissue tumors, modern approach (FISH, RT-PCR), neuroendocrine carcinoma.”
- If you want to expand this list you could also incorporate the names of the various entities as provided in the subtitles such as “dermatofibrosarcoma protuberans, leiomyosarcoma, liposarcoma, Angiosarcoma, Malignant Peripheral Nerve Sheath Tumor, etc”.

B. Zelger
Department of Dermatology and Venerology,
Innsbruck Medical University, Anichstrasse 35,
AT-6020, Innsbruck, Austria
e-mail: Bernhard.Zelger@i-med.ac.at
B. Zelger and O. Bechter

11.5.2 Sarcomas with Fibrocytic Differentiation: Dermatofibrosarcoma Protuberans

Key Features

- Discohesive growth pattern
- Inadequately wide excisions
- Frequent recurrences
- Translocations between chromosome 17 and 22 lead to a fusion gene between COL1A1 and PDGFB
- The fusion product of the translocation activates a tyrosine-kinase and can be inhibited by a synthetic designer drug imatinib

11.5.2.1 Etiology and Pathophysiology

In dermatofibrosarcoma protuberans (DFSP) translocations between chromosome 17 and 22 with or without a ring chromosome 17 have led to a fusion gene between COL1A1 and PDGFB (Fig. 11.5.1).

11.5.2.2 Clinical Characteristics and Diagnosis

Fibrocytic differentiation is characterized by fibrocytes or fibroblasts with variable synthesis of collagen and/or acid mucopolysaccharides (mucin). According to the composition of its various components, these lesions are mostly skin-colored to tan and hard (collagen) and, due to discohesive growth, multilobular; more cellular...
variants appear fleshy (**classic fibrosarcomas** with herringbone pattern), collagen prominent forms, similar to scars and keloids (**desmoids**), myxoid variants, soft, slightly bluish and tightly elastic to cystic (**myxofibrosarcoma**). The stereotypical clinical presentation of various sarcomas with fibrocytic differentiation is given in Table 11.5.2.

### 11.5.2.5 Experimental Approaches

The fusion product of translocations between chromosome 17 and 22 activates a tyrosine-kinase and thereby, stimulates proliferation which may be inhibited by a synthetic designer drug imatinib (Glivec®). Imatinib was originally developed as an inhibitor of CD117 or c-kit, the ligand of a tyrosine-kinase receptor in gastrointestinal stromal tumor, a frequent (malignant) neoplasm deriving from interstitial cells of Cajal, which usually regulate the gastrointestinal motility. Arrest of tumor growth as well as regression were observed in primarily unresectable tumor loads, metastases and other fibrocytic lesions, such as desmoids [6–8].

### 11.5.2.6 Complications to Avoid

Inadequately wide excision at primary presentation leads to frequent recurrences which need huge surgical, disfiguring excisions.

### Take Home Message

- Therapy as early as possible with wide enough margins to avoid recurrences is essential.

### 11.5.2.7 Global Variations

Paradoxically, worldwide recurrence rates are lower among dermatologic surgeons than with plastic and other surgeons who tend to not widely enough excise the primary lesion.

### 11.5.3 Sarcomas with Myogenic Differentiation: Leiomyosarcoma

**Key Features**

- Fleshy-reddish lesions
- Otherwise similar to DFSP, but may be painful
- Inadequately wide excisions
- Frequent recurrences
- More grim prognosis in subcutaneous, recurrent and/or dedifferentiated variants

---

**Fig. 11.5.1** FISH analysis in giant cell fibroblastoma (a DFSP variant) with a “bring together approach” of COL1A1 from chromosome 17q12 (labeled by biotin in green) to PDGFB from chromosome 22q13 (digoxigenin in red)
<table>
<thead>
<tr>
<th>Entity</th>
<th>Stereotypical clinical presentation</th>
<th>Stereotypical pathology</th>
<th>Other characteristics and peculiarities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatofibrosarcoma protuberans (DFSP)</td>
<td>M &lt; F, 4th to 5th decade, trunk (shoulder, groin), extremities, rarely head, multinodular (“promontory-like”) plaque. Rare congenital and infantile variants.</td>
<td>Spindle cell lesion with storiform pattern and lace-like to multilayered, discohesive infiltration of subcutis; positive for CD34. Myxoid, pigmented (Bednar) and sarcomatous variants.</td>
<td>Ring chromosome 17. Cured by wide (2–3 cm) excision, metastases mostly in sarcomatous DFSP.</td>
</tr>
<tr>
<td>Giant cell fibroblastoma</td>
<td>Infantile variant of DFSP.</td>
<td>Pseudovascular clefts with bizarre giant cells.</td>
<td>See DFSP.</td>
</tr>
<tr>
<td>Myxofibrosarcoma</td>
<td>M &gt; F, 6th–8th decade, lower extremities, subcutaneous, multinodular lumps.</td>
<td>Myxoid neoplasm with multilobular-discohesive growth, hyperchromatic spindle to stellate, focally vacuolated (mucin/pseudolipoblasts) cells and curvilinear vessels.</td>
<td>According to grading heterogeneous genetic changes, recurrences and lymph node and lung metastases (up to 50%).</td>
</tr>
<tr>
<td>Low grade fibromyxoid sarcoma (Evans tumor)</td>
<td>M &gt; F, 3rd–4th decade, lower extremities, lumps at or below fascia.</td>
<td>Bland appearance with juxtaposition of fibrous and myxoid areas. Frequently positive for CD34 and EMA (50%). Variant: hyalinizing spindle cell tumor with giant rosettes.</td>
<td>Frequent recurrences, late metastases and death after decades. Wide excision (3–5cm) or amputation.</td>
</tr>
<tr>
<td>Solitary fibrous tumor</td>
<td>M = F, adults, any location including skin and subcutis, well circumscribed nodules.</td>
<td>Patternless pattern, i.e. variation of storiform, keloidal, hemangiopericytoma-like and myxoid areas. Positive for CD34.</td>
<td>Variable prognosis with recurrence and aggressive behavior in 20%.</td>
</tr>
<tr>
<td>Childhood fibrosarcoma</td>
<td>M = F, children, deep soft tissue.</td>
<td>High cellularity with herringbone pattern.</td>
<td>In contrast to adult types excellent prognosis.</td>
</tr>
<tr>
<td>Desmoids</td>
<td>M &lt; F, 3rd–4th decade, extraabdominal (60%) on limb girdles and proximal extremities, head-neck in children; abdominal (25%) post sectio caesarea, and intraabdominal (15%) in Gardner syndrome (familial polyposis coli associated colon carcinoma, osteomata, infundibular cysts).</td>
<td>Keloidal aspect with moderate atypia and irregular infiltrative margins.</td>
<td>Mutations of APC gene causing activation of β-katenin. Frequently misinterpreted as keloid, then recurrent. Exceptional dedifferentiation and metastases.</td>
</tr>
</tbody>
</table>
11.5.3.1 Etiology and Pathophysiology

No characteristic translocations.

11.5.3.2 Clinical Characteristics and Diagnosis

Clinical presentation is similar to DFSP, i.e., multinodular plaques with “promontory” sign, but by variable myogenic fibrils, good vascularization and less/no other stromal components lesions have a more fleshy-red character and as a clue may be painful. Leiomyosarcoma occurs more frequently in males, predominantly in the 5th–7th decade, on the lower extremities followed by the trunk. Each 15% are seen in cutis and subcutis, the rest in deeper soft tissue or internal organs (uterus, large vessels). Histology shows a fascicular growth pattern of elongated cells with cigar-shaped nuclei, eosinophilic (to fibrillary) cytoplasm and a perinuclear halo in an irregular, destructive neoplasm.

11.5.3.3 General Therapeutic Outline

Complete (wide excision) at first presentation. Prognosis correlates with size and location, dermal variants being cured by wide excision, subcutaneous and deeper variants tending to recur (50%), dedifferentiate (with malignant fibrous histiocytoma pattern) and then cause metastases (lung) and death (subcutaneous 30–40%, deeper variants up to 80%).

11.5.3.4 Current Established Therapies

Wide excisions with clinically (up to) 3 cm free margins will avoid recurrences. In areas where this is not possible (e.g., face) or lesions are dedifferentiated Mohs technique and brachytherapy (intraoperative irradiation) must be considered.

11.5.3.5 Experimental Approaches

See therapeutic summary at end.

11.5.3.6 Complications to Avoid

Inadequately wide excision at primary presentation leads to frequent recurrences which need huge surgical, disfiguring excisions.

11.5.3.7 Global Variations

Resection problems similar to DFSP may lead to more frequent recurrences in surgical than dermatologic patients.

Comment: Rhabdomyosarcoma, the most common sarcoma in children and juveniles (20%), rarely affects skin. Most lesions occur in deep soft tissue or submucosal regions of genitalia or ear-nose-throat and then may appear polypoid (botryoid rhabdomyosarcoma). Otherwise, they are typical small-round cell neoplasms (embryonal and spindle cell forms), rarely with rhabdomyoblasts (densely eosinophilic cytoplasm with fibrillary cross striations), characteristically positive for desmin, h-caldesmon and/or myoglobin. In alveolar rhabdomyosarcoma, more common in early adults, a discohesive “alveolar” pattern correlates with characteristic translocations (Table 11.5.1), not seen in embryonal forms, while pleomorphic rhabdomyosarcomas of adults in their fifties are cytogenetically complex and heterogeneous. Combination of surgery and radiochemotherapy has amended 5-year survival rates of embryonal forms (>80%), while prognosis is still poor (50%) for alveolar and even less (<20%) pleomorphic variants.

Take Home Message

- Cutaneous leiomyosarcomas are easily cured by wide excision, subcutaneous and dedifferentiated variants have a grim prognosis.
11.5.4 Sarcomas with Lipogenic Differentiation: Liposarcoma

Key Features

- Rare in skin, mostly subcutaneous
- Frequently in neck-shoulder/extremities of male between 40 and 70 years
- Imitate lipomas and frequently appear lobulated, yellowish, with a characteristic soft consistency
- Subcutaneous variants mostly well-differentiated with good prognosis (atypical lipomatous tumor)
- Not rarely underdiagnosed, then recurrences of “lipomas”

11.5.4.1 Etiology and Pathophysiology

Cytogenetics reveals a ring or giant chromosome 12q13-15 in well-differentiated liposarcoma as well as its dedifferentiated manifestation. Thereby, FISH will reveal an increase of genes coding mdm2 or CK4, whose gene products sometimes can even be detected by immunohistochemistry. Both, myxoid and round cell liposarcomas have a common translocation t(12;16) (q13;p11) [9]. Beside overlapping features in histology these molecular findings proved the common nature of these entities which originally were described as different neoplasms. In contrast pleomorphic liposarcomas are cytogenetically very different and inhomogenous.

11.5.4.2 Clinical Characteristics and Diagnosis

Liposarcomas include a spectrum of variably aggressive neoplasms with lipogenic differentiation, histologically characterized by adipocytes to lipoblasts. Clinically, such lesions frequently appear lobulated, yellowish, with a characteristic soft consistency. Liposarcomas rarely affect subcutis or even skin, but are common in deep soft tissue including fascia and muscle. Most neoplasms occur in the extremities or retroperitoneum of male between 40 and 70 years of age. Lesions develop de novo (not in preexisting lipomas), usually grow slowly and without symptoms and thereby may develop huge masses (20 kg). In skin and subcutis we see nearly exclusively well-differentiated liposarcomas in neck-shoulder-back region or on the extremities. These neoplasms frequently are misdiagnosed clinically and histologically as lipomas, and thus recurrences of a “lipoma” may be a characteristic clue to diagnosis (Fig. 11.5.2).

Histology of liposarcomas is quite variable; hallmark of all forms are hyperchromatic lipoblasts which show a multivacuolated cytoplasm and indented/scalloped nuclei. Myxoid to round cell liposarcomas additionally show a characteristic arborized, chicken-wire-like vasculature.

Fig. 11.5.2 Recurrence (note scar!) of a “lipoma,” a characteristic clue for a well-differentiated liposarcoma
11.5.4.3 General Therapeutic Outline

Complete excision, in high grade variants combined with brachy- and/or adjuvant irradiation.

11.5.4.4 Current Established Therapies

Therapy of (cutaneous) liposarcomas is performed by excision with 1–2 cm free margins. Prognosis correlates with subtype and dedifferentiation, being worst in pleomorphic with 5-year survival rates of 20%, intermediate in myxoid to round cell (myxoid 90%, mixed 40–45% to round cell 25%), and best in well-differentiated liposarcomas with 5-year survival rates of 90% in deep soft tissue, nearly 100% in subcutis.

11.5.4.5 Experimental Approaches

See therapeutic summary at end.

11.5.4.6 Complications to Avoid

According to their biology subcutaneous variants have sometimes been called atypical lipoma or atypical lipomatous tumor, which in our experience is misleading, as in case of mismanagement with incomplete excision frequent recurrences with progressive dedifferentiation may finally cause metastases and death by the neoplasia. Such course of disease is regularly seen due to unresectability in retroperitoneal location and decreases the 5-year survival rates to less than 60%.

Take Home Message

- Most instances of “recurrent lipomas” are primarily misdiagnosed well-differentiated liposarcomas.

11.5.4.7 Global Variations

Not aware to me.

11.5.5 Sarcomas with Vascular Differentiation: Angiosarcoma

11.5.5.1 Etiology and Pathophysiology

So far there is no specific finding in cytogenetics which would reliably classify angiosarcomas.

11.5.5.2 Clinical Characteristics and Diagnosis

Angiosarcomas occur in three characteristic settings: angiosarcomas of the elderly stereotypically affect the scalp and/or upper half of the face of heptagenarian males. They may be misinterpreted as hemorrhage, lymph- or Quincke edema, rosacea, or nevus flammeus. Stewart-Treves syndrome characteristically affects females on the upper limbs following breast surgery with lymph node dissection and/or irradiation within 5–10 years; in rare instances the lower limbs with other causes of lymphedema such as congenital or lymphovenous, may also affect male patients. Finally, post irradiation angiosarcoma affects patients 5–10 years after irradiation, mostly on the trunk (breast and upper trunk in mammary, lower abdomen and genitalia in genitourinary carcinomas). Histology reveals a vascular malignancy with dissection of preexisting
connective tissue by slit-like spaces, sometimes with prominent ectasia and hemorrhage (Fig. 11.5.3). The cells are atypical, show variable mitoses and necroses and are demarcated by an irregular infiltrate of lymphocytes and frequently plasma cells.

11.5.5.3 General Therapeutic Outline

A multidisciplinary approach by surgery and radiochemotherapy

11.5.5.4 Current Established Therapies

Despite a multidisciplinary approach with surgery, radiochemotherapy and modern biologicals (bevacicumab, an anti-VEGF antibody; Avastin®) prognosis of angiosarcoma is poor with less than 20% 2–5 year survival rates. The only reliable parameter correlated with a bit better prognosis is a size of less than 4 cm at the time of diagnosis. While nowadays the evidence, that Morbus Kaposi (“Kaposi sarcoma”) is a reactive-inflammatory response to HHV8 and not a sarcoma, seems convincing [12], there are numerous other vascular lesions which have been considered as low grade vascular neoplasms or “hemangioendotheliomas.” Clinicopathologic features and their present nosologic status are summarized in Table 11.5.3.

11.5.5.5 Experimental Approaches

Modern biologicals (bevacicumab, an anti-VEGF antibody; Avastin®) have so far been of limited value.

11.5.5.6 Complications to Avoid

In some instance lesions may be well-differentiated and such lesions have in post irradiation cases not infrequently been misdiagnosed as atypical post irradiation vascular lesions [10, 11].

Take Home Message

- One of the most highly aggressive neoplasms of mankind.
### Table 11.5.3 Clinical and histological characteristics of hemangioendotheliomas

<table>
<thead>
<tr>
<th>Type of hemangioendothelioma</th>
<th>Age (years)</th>
<th>Location</th>
<th>Histologic features</th>
<th>Recurrence or metastasis</th>
<th>Dignity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retiform hemangioendothelioma</td>
<td>Adults, 20–40</td>
<td>Extremities</td>
<td>Arborizing vessels reminiscent of rete testis, hobnail endothelium</td>
<td>Often recurrence/one single lymph node metastasis (of a biphasic RH)</td>
<td>Low grade Malignant vascular neoplasm, angiosarcoma</td>
</tr>
<tr>
<td>Epithelioid hemangioendothelioma</td>
<td>Adults of all ages, rarely in children</td>
<td>Skin, liver, bone, lung</td>
<td>Nest and cords of epithelioid endothelial cells, characteristic cytoplasmatic vacuoles, myxohyaline stroma</td>
<td>20–30% metastases, neoplasia related death in 15%</td>
<td>High grade (G2) Malignant vascular neoplasm, angiosarcoma</td>
</tr>
<tr>
<td>Kaposiform hemangioendothelioma</td>
<td>Infants and children</td>
<td>Trunk and extremities</td>
<td>Tightly packed spindle cells, irregular slit-like vascular spaces (reminiscent to Morbus Kaposi)</td>
<td>Locally ill-defined, no metastases, complicated by coagulopathy (Kasabach-Merrit syndrome), lymphangiomatosis</td>
<td>Congenital hamartoma or malformation</td>
</tr>
<tr>
<td>Spindle cell hemangioma (previously hemangioendothelioma)</td>
<td>All ages</td>
<td>Distal extremities</td>
<td>Intravascular lesion with collapsed vascular spaces separated by spindly fibroblasts without atypia, multifocal or contiguous process</td>
<td>Recurrence often, no metastases (one case of lymphnode metastasis following irradiation in the original report)</td>
<td>Benign vascular neoplasm or malformation, hamartoma</td>
</tr>
<tr>
<td>Polymorphous hemangioendothelioma</td>
<td>Adults, 20–50</td>
<td>Lymph nodes, one case in deep soft tissue (paravertebral region)</td>
<td>Primitive solid vascular and ectatic angiomatous structures formed by uniform, polygonal cells</td>
<td>Rarely recurrence and metastases (one report of lung metastasis)</td>
<td>Low grade malignant vascular neoplasm, angiosarcoma</td>
</tr>
<tr>
<td>Composite hemangioendothelioma</td>
<td>Adults, 20–70</td>
<td>Hands and feet</td>
<td>Complex admixture of predominantly epithelioid, retiform, spindle cell and angiosarcoma-like elements</td>
<td>Recurrence often, rarely metastases</td>
<td>Low grade malignant vascular neoplasm, angiosarcoma</td>
</tr>
</tbody>
</table>
11.5.5.7 Global Variations

Caucasians seem to be more prominently involved than other races.

11.5.6 Sarcomas with Neural Differentiation: Malignant Peripheral Nerve Sheath Tumor

11.5.6.1 Etiology and Pathophysiology

This group includes soft tissue neoplasias with schwannian or, rarely, perineural differentiation. The former are best termed neurogenic, the latter perineurial sarcomas. Other terms are less precise such as malignant peripheral sheath tumor which includes both schwannian and perineural malignancies and may be found in central location, too; or malignant schwannoma which is an oxymoron as a schwannoma by definition of a benign neoplasia cannot at the same time be malignant; or neurofibrosarcoma, which is too closely associated with von-Recklinghausen neurofibromatosis and thereby ignores that roughly 50% of neurogenic sarcomas occur outside this phakomatosis. Cytogenetically, one frequently sees a deletion of NF1 gene on chromosome 17, responsible for a tumor suppressor gene, together with a complex and genetically very instable karyotype [14].

11.5.6.2 Clinical Characteristics and Diagnosis

Neurogenic differentiation histologically shows wavy to zig-zac-like schwann cells with very long, slim extensions of cytoplasm, occasionally forming myelin sheaths, fine fibrillar, ultrastructurally long spacing collagen and mucin [13]. Accordingly, neurigenic sarcomas in early stages clinically are skin-colored to bluish, frequently soft, in association or connection with a preexisting nerve, neurofibroma or in patients with neurofibromatosis, in later dedifferentiated, highly cellular stages more fleshy-reddish and ulcerated. Sporadic neurogenic sarcomas usually occur in the 5th decade without sexual predilection; in neurofibromatosis 10–15 years earlier and more commonly in male (lifetime risk of 2%); or a latency of 10 years following irradiation. The extremities followed by trunk and rarely the head are affected in order of decreasing frequency. Such patients usually develop rapidly growing tumors, most commonly not in the dermis, but in deep soft tissue or subcutis. Lesions usually are asymptomatic and thus frequently develop huge dimensions (5–10 cm and even larger). Histology reveals an ill-defined, fascicular neoplasm with geographical necroses sparing perivascular areas. Perivascular and peri/intraneural spread is a clue for the diagnosis of a neurogenic sarcoma as are palisading and S100 protein reactivity. According to differentiation such features are frequently missing and only seen in better differentiated or only focally in dedifferentiated tumor parts and this correlates with ultrastructural schwannian differentiation.

11.5.6.3 General Therapeutic Outline

A multidisciplinary approach by surgery and radiochemotherapy.

11.5.6.4 Current Established Therapies

Despite radical surgery with 3–5 cm clinically uninvolved margins prognosis is poor, mostly due to
discohesive, neuro- and angiotropic tumor spread. The 5-year survival for sporadic forms is 50%, in neurofibromatosis 20–25%, and in post irradiation variants 10–15%.

### 11.5.6.5 Experimental Approaches

See therapeutic summary at end.

### 11.5.6.6 Complications to Avoid

Regular follow-up of NF patients should help to as early as possible recognize those patients who develop neurogenic malignancies. The best chance to cure this disease is by early wide excisions.

### 11.5.6.7 Global Variations

The few reports of **perineurial sarcomas** revealed no stereotypical clinical profile. Perineurial differentiation reveals spindly cells with long dendrites forming onion-like aggregates, sometimes with central calcification (psammoma bodies), positive for epithelial membrane antigen (EMA), negative for S100 protein and glial fibrillary acid protein, and ultrastructurally with basal lamina and desmosomes. There is relationship to **meningiomas** as perineurial cells are the peripheral extensions of central meningothelial cells.

**Comment:** Chondro- and osteosarcomas are malignant neoplasias with chondroid and/or osseous differentiation and thus of hard consistency. Primary forms of these sarcomas outside the skeleton in soft tissue are exceptional, exceedingly rare in the skin. In most instances metastatic cartilage and bone formation is seen in liposarcoma, neurogenic sarcoma, melanoma or squamous cell carcinoma.

### 11.5.7 Sarcomas of Uncertain Differentiation

This is a heterogeneous group of well-defined clinicopathologic entities, whose differentiation is unclear or controversial. The three most relevant are:

#### 11.5.7.1 Atypical Fibroxanthoma

In our interpretation atypical fibroxanthoma is no disease, but a *reaction pattern* of a pleomorphic anaplastic, sometimes spindly, superficial and thus frequently exophytic eroded to crusted malignant neoplasia. A nodule to tumor characteristically develops within weeks to months clinically similar to dedifferentiated squamous cell carcinoma and frequently associated with squamous cell carcinoma in situ, type actinic keratosis. In our experience the vast majority of these lesions are indeed **squamous cell carcinomas**, which have (mostly) lost their capacity to synthesize keratins. Due to tissue necrosis by the rapidly growing dedifferentiated neoplasm reactive macrophages are common. This complex situation has lead to the misperception of a macrophage lesion (“xanthoma”). Similar patterns can rarely be seen in melanoma, basal cell carcinoma, and superficial sarcomas [15].

Characteristically, neoplastic cells loose reactivity for keratins (or other proteins such as desmin or S100 protein) and only stain for vimentin, the basic structure of cytoskeleton. Sometimes, morphologically analogous lesions still express keratins, either diffuse or focally (then called *dedifferentiated* or *spindle cell squamous cell carcinomas*); in some cases serial sections will reveal small foci of keratin reactivity or transition from a more common form of squamous cell carcinoma into AFX. Molecular biology, too, frequently detects chromosomal defects similar to those in squamous cell carcinomas such as p53 or p24 mutations. Complete excision cures the lesion, only rarely metastases to lymph...
nodes and beyond are found, mostly in those lesions which are not restricted to dermis, but broadly affect subcutis or even deeper tissue (and then follow the biology of malignant fibrous histiocytoma).

11.5.7.2 Epithelioid Sarcoma

This rare sarcoma characteristically affects adolescents and young adults, male more common than female, and has an acral predilection (fingers, hand, toes, feet, limbs). A skin-colored, multinodular, hard and sometimes exulcerated lump usually arises in subcutis, rarely dermis. The neoplasm grows slowly and discohesively, which leads to locoregionary spread along preexisting structures such as tendons, nerves or vessels. Despite wide excision margins this phenomenon frequently causes recurrences, later on lymphogenic and hematogenic spread (lung). Histology shows nodules of epithelioid cells with central necroses imitating granulomas (classical miscue granuloma anulare). Atypia, necroses, and mitoses are common. Immunohistochemistry is positive for keratin markers, frequently (60%) also for CD34. The best chance of cure is wide excision with 5 cm free margins, frequently amputation. 5-year survival is more than 90%, yet 20-year survival less than 20%.

11.5.7.3 Clear Cell Sarcoma

This lesion, also known as malignant melanoma of soft parts, shows all characteristics of a melanoma except a highly characteristic chromosomal translocation t(12;22)(q13;q12) so far never seen in melanoma [16]. Clinically, clear cell sarcoma occurs in soft tissue (fascia, tendons) and forms a skin-colored tan to slightly bluish, ill defined nodule or tumor which most commonly occurs in adults (3rd–4th decade), male more common than female, with predilection of extremities, in particular feet and hands. Histology reveals nests and sheaths of clear to eosinophilic cells with scattered giant cells, positive for S100 protein and with Melan A und HMB45. Usually there is no connection to the epidermis. Despite wide excision metastases are common (50%) first to lymph nodes, later to lung with final death due to progression.

11.5.8 Neuroendocrine Carcinoma

11.5.8.1 Etiology and Pathophysiology

Neuroendocrine carcinoma (synonyms: Merkel cell carcinoma, trabecular carcinoma) is a rare, highly aggressive, small round cell neoplasm of the skin. Differentiation is characterized by electron dense neuroendocrine granules ultrastructurally, alike those in Merkel cells, the only member of the APUD system (amine precursor uptake and decarboxilation system) in the skin.

11.5.8.2 Clinical Characteristics and Diagnosis

Their incidence ranges from 0.1 to 0.3/100,000 people and year. Most commonly males and females in their 6th and 7th decade present with lumps on the head-face-neck, which have a characteristic lilac color and a fleshy consistency (Fig. 11.5.4). Histology is characterized by strands, nests and sheaths of a small round cell neoplasm with round hyperchromatic nuclei and a small rim of bluish cytoplasm. Lesions are highly mitotic, well vascularized and with (numerous) single cell necroses. Lesions may rarely be seen intrepideral, are mostly dermal and may extend into subcutis and deep soft tissue. Immunohistochemically, lesions are positive for keratins and neuroendocrine markers (neuron specific enolase, chromogranins, vasoactive intestinal peptide) frequently with a characteristic paranuclear dot-like pattern (in particular for cytokeratin 20).
**11.5.8.3 General Therapeutic Outline**

Prognosis varies according to extension. Recurrences are frequent, at presentation one third already has lymph node metastases which in due course increases to 60%, and wide spread metastases with death within a few months is seen in 30%.

**11.5.8.4 Current Established Therapies**

Therapy includes wide excision of primary lesions with 3 cm free margins. Similarly, recurrences and locoregionary metastases are excised; as the neoplasm is highly radiosensitive adjuvant irradiation with up to 50 gray is recommended.

**11.5.8.5 Experimental Approaches**

See therapeutic summary at end.

**11.5.8.6 Complications to Avoid**

Differential diagnosis includes all other cutaneous small round cell neoplasms (synovial sarcoma, rhabdomyosarcoma, extraskeletal mesenchymal chondrosarcoma, neuroblastoma; lymphoma, small cell melanoma, small cell squamous cell carcinoma and basal cell carcinoma) and metastases from primary extracutaneous neuroendocrine carcinomas (which usually are negative for cytokeratin 20).

**11.5.9 General Therapeutic Guidelines**

Although surgery is the mainstay of treatment of soft tissue sarcomas (STS) of the skin, systemic treatment might have to be included into the treatment process in a given situation. Systemic treatment can either be given adjuvant after topical therapy, where cure is the therapeutic goal, or in a palliative situation, where symptom control through tumor growth control is the main intent of treatment. There are several chemotherapeutic agents reported to be active in STS with response rates up to 40%. Among other factors, the response rate correlates with the dose of a given cytostatic drug applied as well as with the grading of the tumor. In general, low grade lesions tend to be less sensitive to cytostatic treatment compared to high grade lesions. Most clinical trials tested either doxorubicin (response rates 5–40%) or ifosfamide (response rate 20%). Other agents like methotrexate, cisplatin and cyclophosphamide have a response rate of approximately 15%, whereas newer cytostatic drugs like taxanes, vincaloids and gemcitabine showed to be modestly active, usually with response rates below 10%.

**11.5.9.1 Adjuvant Chemotherapy**

The rationale for applying systemic therapy after a curatively performed surgical approach is to minimize...
the risk of relapse. This rationale is emphasized by the fact that almost 50% of patients develop metastatic disease despite sufficient topical tumor control [17]. In addition, adjuvant treatment is well established in rhabdomyosarcomas, Ewing sarcomas and osteosarcomas providing a proof of principle for the benefit of treating minimal residual disease after surgery in per se chemosensitive sarcomas. Since doxorubicin and ifosfamide are the most active drugs numerous trials published made use of these cytostatic compounds. Randomized trials of adjuvant chemotherapy after surgery suggested an improvement in 5 years disease free survival as well as a significant overall survival benefit [18, 19]. The absolute overall survival benefit deriving from adjuvant chemotherapy was 13% at 2 years and only present in patients with high risk sarcomas of the extremities. A similar result was obtained in another trial, again including patients with high grade lesions [20].

Despite the favorable findings of adjuvant treatment in the trials mentioned other trials have failed to demonstrate a treatment benefit. In a meta-analysis of existing randomized trials including 1568 patients, the likelihood of disease recurrence was decreased by 10% at 10 years with a nonsignificant absolute survival benefit of 4% at 10 years. Subgroup analysis failed to provide evidence that different STS entities had a substantially different benefit from adjuvant chemotherapy; however a trend was seen for a small benefit in patients with sarcomas of the extremities [21]. Several reasons can explain the controversial issue of adjuvant chemotherapy in soft tissue sarcomas. Most trials contain only a small number of patients resulting in a low statistical power to detect a meaningful therapeutic benefit. Different inclusion criteria with regard to tumor size and grading as well as different chemotherapy regimens have been applied. Furthermore soft tissue sarcomas encompass a very heterogeneous group of diseases where chemosensitivity varies among different entities; e.g., leiomyosarcoma generally respond to chemotherapy whereas neurofibrosarcomas are fairly insensitive to cytostatic drugs [22]. Therefore, adjuvant chemotherapy can not be considered as standard care in patients with soft tissue sarcoma. High risk patient with large extremity neoplasias, deep localization and unfavorable grading might benefit from adjuvant therapy. The rather small benefit however has to be balanced against toxicity and therefore treatment has to be determined on an individual basis.

### 11.5.9.2 Palliative Chemotherapy

In patients with overt metastatic disease, chemotherapy can be offered incurable as a palliative treatment option. It is essential that the toxicity accompanied with this approach is balanced against the potential clinical benefit achieved by tumor regression. Cytostatic drugs commonly used for palliative treatment include doxorubicin, cyclophosphamide, ifosfamide, methotrexate, vincristine, cisplatin, dactinomycin and dacarbazine.

Doxorubicin is an agent, which clearly shows antitumor activity in soft tissue sarcomas. Response rates are observed in 16–27% of the patients and the median overall survival ranges from 7.7 up to 12 months [23]. Ifosfamide is the second drug that is active in this group of diseases. Anti-tumor activity is similar with about 25% of patients showing an overall response rate. Since there are no randomized trials comparing single agent doxorubicin and ifosfamide, ifosfamide seems to be a valid option in patients for whom anthracyclin therapy is contraindicated. All other drugs mentioned have only modest activity with response rates of 10% or lower.

Since a rapid tumor response alleviates tumor associated symptoms best, combination chemotherapy has been explored in a numerous trials. Unfortunately, most combinations have not been assessed in a randomized fashion, making it difficult to draw conclusions about their efficiency compared to lesser toxic single agent therapies [24]. Available data show that doublet combinations are not superior to doxorubicin monotherapy, but are actually known to be more toxic. Only two combinations seem to have a higher response rate compared to the single agent regimen. Doxorubicin/ dacarbazine and doxorubicin/ifosfamide combinations result in response rates of approximately 30%, however this higher activity does not translate into a survival advantage whereas toxicity is significantly increased in the combination arm [25, 26]. In a meta-analysis of doxorubicin combination chemotherapy compared to monotherapy the higher response rates gained with the combination therapy did not reach statistical significance. Also the overall survival at 1 and 2 years did not differ between the two regimens [27]. Other randomized trials comparing various doxorubicin combinations also failed to show a survival advantage. Therefore currently available data do not support the application of combination chemotherapy in patients with metastatic soft tissue sarcoma but
suggest doxorubicin monotherapy as the standard treatment.

Despite the fact that high tumor grading is appreciated as a favorable predictor for chemotherapy response, the histological subtype has not been identified as an important independent discriminator for chemotherapy efficacy [28]. Nevertheless several indications exist, that different subtypes respond differently to chemotherapy. For instance paclitaxel which is considered to be fairly inactive in soft tissue sarcomas showed promising activity in the subgroup of patients with angiosarcoma of the scalp [29]. Similar the combination of gemcitabine and paclitaxel showed a remarkable overall response rate of 53% even in patients failing first line doxorubicin chemotherapy [30]. Despite these interesting findings, one should emphasize that none of these treatments have been evaluated in a randomized fashion yet.

11.5.9.3 Experimental Approaches

Novel therapeutic approaches aim at targeting vital molecular pathways of neoplastic cell survival. Several tumor entities show characteristic alterations of distinct pathways. By blocking such pathways, one can expect that these strategies might elicit a more tumor specific, hence less toxic, effect. Whereas in other solid neoplasms, molecular therapies are more and more applied in a clinical setting, they are still in their infancy with regard to soft tissue sarcomas. Data showing overexpression of the epidermal growth factor receptor and the association of vascular endothelial growth factor expression with a poorer prognosis provide hints for the presence of a rational for a molecular therapy in STS [31, 32]. Trials in which tumor angiogenesis is tackled with bevacizumab or with pan tyrosin kinase inhibitors are on their way [33]. The serine-threonine kinase mTOR plays a crucial role in intracellular signal transduction. Its inhibition has shown promising anti-tumor activity in heavily pretreated patients with soft tissue sarcomas. In a large phase II trial stable disease or partial responses were achieved in approximately 30% of the patients resulting in a median overall survival of 40 weeks [34].

The great challenge in the future will be to incorporate molecular targeted therapies into conventional treatment regimens. Due to the plethora of molecular pathways and the variety of different drugs available today, this task will be substantial. The conduction of hypothesis driven clinical trials based on a strong molecular rational will be required in order to significantly improve systemic treatment options in patients with STS.

Acknowledgment The author is thankful to Maria Debiec-Rychter, University of Leyden, Belgium, for providing the FISH analysis in Fig. 11.5.1.

References

27. Bramwell VHC et al (2001) Doxorubicin-based chemotherapy for palliative treatment of adults with locally advanced or metastatic soft tissue sarcoma. The Cochrane Database of systematic reviews 4
33. Sleijfer S et al (2007) Phase II study of pazopanib (GW786034) in patients (pts) with relapsed or refractory soft tissue sarcoma (STS): EORTC 62043. 2007 ASCO Annual meeting proceedings part I: 10031
34. Chawla SP et al. (2007) Survival results with AP23573, a novel mTOR inhibitor, in patients (pts) with advanced soft tissue or bone sarcomas: update of phase II trial. 2007 ASCO Annual meeting proceedings part I: 10076
Part XII

Miscellaneous Disorders
12.1 Skin diseases in pregnancy can be categorized as follows:

- Preexisting skin diseases affected by pregnancy, the most common being atopic dermatitis.
- Conditions that cause pruritus but no skin lesions, such as intrahepatic cholestasis of pregnancy.
- Specific dermatoses of pregnancy.

### Key Features

- Atopic dermatitis is the most common dermatosis in pregnancy whereas PUPPP is the most common specific dermatosis of pregnancy.
- Increased levels of serum bile acids is the hallmark of intrahepatic cholestasis of pregnancy; ursodeoxycholic acid is the first-line treatment for moderate to severe cholestasis.
- Positive direct skin immunofluorescence is the hallmark of herpes (pemphigoid) gestationis; systemic steroids are the first-line treatment for pemphigoid gestationis.
- PUPPP starts most commonly in the abdominal striae and shows periumbilical sparing associated with multiple gestation pregnancy.
- Fetal risks in intrahepatic cholestasis include distress, stillbirth, and preterm delivery, and the same in pemphigoid gestationis include small-for-gestational age infants, preterm delivery, and neonatal pemphigoid gestationis.
- PUPPP, prurigo gestationis, and pruritic folliculitis of pregnancy present with no maternal or fetal risks, and their etiopathogenesis remains elusive.

### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HG</td>
<td>Herpes (pemphigoid) gestationis</td>
</tr>
<tr>
<td>ICP</td>
<td>Intrahepatic cholestasis of pregnancy</td>
</tr>
<tr>
<td>PP</td>
<td>Prurigo of pregnancy</td>
</tr>
<tr>
<td>PFP</td>
<td>Pruritic folliculitis of pregnancy</td>
</tr>
<tr>
<td>PUPPP</td>
<td>Pruritic urticarial papules and plaques of pregnancy</td>
</tr>
<tr>
<td>UDCA</td>
<td>Ursodeoxycholic acid</td>
</tr>
</tbody>
</table>

### 12.1.1 Atopic Dermatitis

#### 12.1.1.1 Etiology and Pathophysiology

The reasons why atopic dermatitis (AD) (also known as atopic eczema) is more prevalent or flares more often during pregnancy remain unclear. Some authors speculated that the placental Th-2 drive, which is associated with an increase in interleukin-4 during gestation, may be critical to the induction of IgE that could be relevant to atopic disease in pregnancy [33]. Nevertheless, the regulation of IgE in normal pregnancy has not been clarified [12].
12.1.1.2 Clinical Characteristics and Diagnosis

AD is the most common pregnancy dermatosis, accounting for 36–49.7% of total cases [2, 72]. AD is more likely to worsen (52%) than remit (24%) [39] in pregnancy, and can occasionally develop for the first time in gestation. There is a personal history of atopy in 27% of pregnant females with AD, a family history of atopy in 50% of cases, and infantile eczema in 19% of the offsprings [73]. The clinical features of gestational AD are identical to those seen in nonpregnant females. Most patients present with flexural eczema on the extremities [72] although eczematous lesions on the trunk are not uncommon. Less common are palmo-plantar pompholyx eczema, follicular truncal, and facial eczema. Eczematous lesions can develop bacterial or herpetic superinfection in pregnancy.

12.1.1.3 General Therapeutic Outline

Gestational AD is usually treated with a moisturizer, a low- to mid-potent topical steroid, and an oral antihistamine for symptomatic relief. Dry skin care should be thoroughly reviewed with the patient.

12.1.1.4 Current Established Therapies

Mid- or high-potent topical steroids can be used for severe symptomatic eczema but when they are used on large body surface areas there is systemic absorption and the risks approximate those observed with systemic steroids. A short course of oral steroid may be required for severe symptomatic or generalized eczema. The newer topical immunomodulators (pimecrolimus, tacrolimus) are Pregnancy Category C. Systemic antihistamines, such as diphenhydramine (Category B), are often required for severe pruritus. Ultraviolet light B (UVB) is a safe adjunct in the treatment of severe chronic eczema. Systemic antibiotics, such as erythromycin base or penicillin, are necessary in superinfected eczema. For herpetic eczema, the risk of fetal damage by acyclovir must be balanced against the risk of intrauterine herpes simplex infection. Most authors recommend that acyclovir be used only for disseminated herpetic infections during pregnancy.

12.1.1.5 Complications to Avoid

There have been no adverse effects on the fetal outcome. Pregnant women who use large amounts of topical corticosteroids over large body surface areas should be warned of the possibility of low-birth-weight babies. Genetic and pre- and perinatal influences, such as Black and Asian race/ethnicity, male gender, higher gestational age at birth, and family history of atopy, particularly maternal history of eczema, have been associated with increased risk of AD in the first 6 months of life [55]. Maternal atopy poses a higher risk for infantile AD than does paternal atopy [65], and in one study [53], the maternal but not paternal total IgE level correlated with elevated infant IgE levels and infant atopy. The influence of breastfeeding on AD in the infant has been debated. Some studies [37] showed no effect on the development of AD, whereas other studies showed significantly lower [10] or increased prevalence [5] of infantile eczema with each additional month of breastfeeding. One of the most important problems in previous studies is confounding by other lifestyle factors. The influence of maternal food antigen avoidance during pregnancy and lactation on the incidence of AD in infants has been also debated [9, 28]. Maternal smoking may be implicated in the development of AD during pregnancy and lactation [66].

12.1.1.6 Global Variations

The largest studies on the prevalence of AD in pregnancy were performed in Europe [2, 72]. These studies
679

Diseases of Pregnancy and Their Management

indicated an unexpectedly high incidence of AD, including new eczema, in gestation. There is no data regarding the prevalence of AD in pregnancy in other ethnic groups.

12.1.2 Pruritus in Pregnancy

Pruritus has been reported in up to 17% of pregnancies. Determining the cause of pruritus and reaching management decisions requires the constellation of clinical and laboratory data often starting from a broad differential diagnosis. First, skin diseases that are not specific to pregnancy, such as AD and scabies, need to be ruled out as well as systemic disorders with skin manifestations, such as autoimmune and infectious diseases, and systemic diseases that cause pruritus but no eruption (lymphoma, liver, renal, and thyroid disease). The presence of jaundice provides a clue to hepatitides or other liver diseases or intrahepatic cholestasis of pregnancy. Conditions specifically related to pregnancy, such as intrahepatic cholestasis, hyperemesis gravidarum complicated with cholestasis, and striae gravidarum can cause pruritus in the absence of skin or systemic manifestations. In cases presenting with pruritus and eruption, one should consider specific dermatoses of pregnancy (reviewed in Sect. 12.1.3), drug eruptions, and hypersensitivity reactions.

12.1.2.1 Intrahepatic Cholestasis of Pregnancy

12.1.2.1.1 Etiology and Pathophysiology

The etiology of intrahepatic cholestasis of pregnancy (ICP) is ambiguous, and current investigations suggest a possible interaction among hormonal, immunologic, genetic, environmental, and probably alimentary factors [44]. Estrogens interfere with bile acid secretion. Progestins inhibit hepatic glucuronyltransferase and the increased sulfated progesterone metabolites, especially the 3α, 5α isomers, may saturate the maximal transport capacity of the hepatocyte. A study [61] showed an enhanced cell-mediated (Th1 type) reaction in ICP that may disturb the immune tolerance balance between mother and fetus. Genetic factors have been suggested by the observed clustering of the condition within families and certain ethnic groups (e.g., Araucanian Indians), worldwide variations, and a higher prevalence of ICP in mothers of patients with progressive familial intrahepatic cholestasis or benign recurrent intrahepatic cholestasis. Notably, several women with ICP have been positive for a heterozygous missense mutation of the MDR3 gene [15], a gene that encodes the canalicular phosphatidylcholine translocase.

12.1.2.1.2 Clinical Characteristics and Diagnosis

ICP is the most common pregnancy-induced liver disorder and occurs predominantly during the third trimester [43]. It is characterized by generalized, usually severe pruritus, elevation of serum bile acids, and mild elevations of other liver function tests. The condition manifests itself with jaundice (intrahepatic jaundice of pregnancy or obstetric cholestasis) or without (pruritus gravidarum). There is a family history in half of the cases and associations with multiple gestation pregnancy [44] and hepatitis C [48]. ICP can recur in 40–60% of subsequent pregnancies or with oral contraceptives [45].

Pruritus usually presents after 30 weeks gestation and often precedes the laboratory abnormalities of the condition; it affects the palms and soles and extends to the legs and abdomen. Excoriations are invariably seen but no primary skin lesions. Mild nausea and discomfort in the upper right quadrant may accompany the pruritus. Mild jaundice (20%) can develop by 2–4 weeks of the onset of pruritus and may be associated with subclinical steatorrhea and increased risk of hemorrhage [45]. ICP may be preceded by a urinary tract infection that may precipitate the onset of this syndrome. Up to 50% of patients develop darker urine and light-colored stools. The elevation of serum bile acids, predominantly the conjugated fraction, is the most sensitive biochemical marker of ICP [45, 48] and correlates with the severity of pruritus. Biochemical characteristics are those of a cholestatic syndrome, and include a mild elevation of transaminases, alkaline phosphatase, cholesterol and triglycerides; the conjugated bilirubin is elevated (2–5 mg/dL) in jaundiced patients. Malabsorption of fat may cause vitamin K deficiency and a prolonged prothrombin time. The symptoms and laboratory abnormalities of ICP typically resolve within 2–4 weeks postpartum.
12.1.2.1.3 General Therapeutic Outline

The objective of pharmacologic treatment is to decrease maternal symptomatology and enhance fetal outcome. Symptomatic treatment with topical antipruritics, emollients, and oral antihistamines is rarely effective; treatment with oral medications (discussed below) is invariably required.

12.1.2.1.4 Current Established Therapies

Epomediol, silymarine, S-adenosyl-L-methionine, activated charcoal, and phenobarbital have met limited success [44, 47]. UVB has shown some response in case reports. Dexamethasone suppression of fetoplacental estrogen production was effective in an uncontrolled study [29] and a case series [14]. Nevertheless, in a recent randomized placebo-controlled trial [25] dexamethasone yielded no alleviation of pruritus or reduction of serum levels of alanine aminotransferase and was less effective than ursodeoxycholic acid (UDCA) at reducing bile acids and bilirubin (Table 12.1.1). Cholestyramine (up to 18 g/day) can be effective in mild to moderate ICP [44] but needs to be administered for several days before a clear benefit for pruritus can be obtained, and is often associated with rebound of pruritus after the first week of treatment. Furthermore, cholestyramine does not improve the biochemical abnormalities of ICP [47], and as it can precipitate vitamin K, it should be administered in conjunction with weekly vitamin K supplementation [44].

The main drug that is currently prescribed for ICP and has the most benefit for mother and fetus is UDCA, which reduces bile acid levels in cord blood, colostrum, and amniotic fluid. UDCA exerts its beneficial effects in a multitude of mechanisms, including stimulation of impaired hepatocellular secretion, reduction of oxidative stress and apoptosis in the placenta (reported in ICP), and restoration of placenta’s impaired ability to carry out vectorial bile acid transfer. Our meta-analysis [45] of randomized controlled trials indicated that UDCA (450–1,200 mg/day) is highly effective in alleviating the pruritus and normalizing the laboratory abnormalities associated with ICP [48, 57]. UDCA has been more effective than S-adenosyl-L-methionine [22, 57] and in several studies has shown a synergistic effect with it [6, 57, 63] (Table 12.1.1). UDCA has been safe for both mother and fetus, and decreases the fetal risks associated with ICP [13]. Compared to cholestyramine, UDCA is safer, works faster, has a more sustained effect on pruritus, and shows higher efficacy in improving the liver function abnormalities of ICP [44]. In addition, babies are delivered closer to term by patients treated with UDCA than those treated with cholestyramine [41] (Table 12.1.1).

12.1.2.1.5 Complications to Avoid

Fetal risks in ICP include distress, stillbirth, meconium-stained amniotic fluid, and preterm delivery associated with an increased prevalence of c-section; these risks correlate to the levels of serum bile acids. The frequency of these risks in a recent British study [40] was lower than that historically reported. The aforementioned complications are related to a decreased fetal elimination of toxic bile acids that can cause vasoconstriction of human placental chorionic veins and increased myometrial contractility; the latter may explain the increased prevalence of preterm delivery in ICP [24]. The effects of bile acids on gut motility and their presence in meconium may explain the observed umbilical vein constriction meconium causes. Whether, however, the cause of intrauterine deaths is chronic placental insufficiency or a sudden acute anoxic event has been debated [40]. Malabsorption of vitamin K increases the risk of intracranial hemorrhage and most authors advocate prophylactic administration of vitamin K. The risk of serious fetal complications makes intensive fetal surveillance mandatory. Many different protocols for intensified surveillance have been proposed. Many authors recommend fetal surveillance, including cardiotocographic monitoring, from the 34th week of gestation [55]. If gestational age is less than 36 weeks, one should monitor bile acids and liver function tests and consider treatment with UDCA as well as delivery at 36–37 weeks with fetal maturity or continue surveillance if liver function tests improve. If gestational age is more than 36 weeks, amniocentesis and delivery should be considered if cervix is favorable and fetal lung maturity is satisfactory. Although active management reduces perinatal mortality in ICP, some authors [40] have argued that the iatrogenic adverse events associated with active management may be equivalent to the perinatal risk posed by cholestasis with intensive surveillance and spontaneous onset of labor.
### 12.1.1 Randomized controlled trials comparing UDCA with other pharmacologic agents in cholestasis of pregnancy

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Control subjects</th>
<th>Dose</th>
<th>Length of treatment</th>
<th>Results</th>
</tr>
</thead>
</table>
| Glantz et al. [25] | 47 UDCA  | 36 dexamethasone  | UDCA: 1 g p.o.qd  
Dexamethasone: 12 mg p.o.q.d. × 1 week then placebo × 2 weeks | 3 weeks             | Marked relief of pruritus and marked reduction of BAs only with UDCA; dexamethasone less effective than UDCA in reducing BAs and bilirubin |
| Nicastri et al. [57] | 4 UDCA   | 4 SAM-e          | UDCA: 300 mg p.o.b.i.d.                   | 20 days             | Pruritus and LFTs significantly improved over placebo or SAM-e                               |
|                  | 4 UDCA   | 4 placebo        | SAM-e: 400 mg i.v.b.i.d.                 |                     | UDCA + SAM-e better than either one alone                                                  |
| Floreni et al. [22] | 10 UDCA  | 10 SAM-e         | UDCA: 450 mg p.o.q.d.  
SAM-e: 1,000 mg i.m.q.d. | 15 days             | Pruritus and BAs significantly improved over SAM-e                                           |
SAM-e: 500 mg i.vbid × 12 days then p.o. | Until delivery | All Rxs improved pruritus; combined Rx improved BAs and transaminases over SAM-e, decreased faster BAs and transaminases over UDCA |
| Roncaglia et al. [63] | 24 UDCA  | 22 SAM-e         | UDCA: 300 mg p.o.b.i.d.  
SAM-e: 500 mg p.o.b.i.d. | Until delivery | Both improved pruritus; LFTs and BAs significantly improved over SAM-e                      |
| Kondrackiene et al. [41] | 42 UDCA  | 42 cholestyramine | UDCA: 8–10 mg/kg p.o.q.d.  
Cholestyramine: 8 g p.o.q.d. | 14 days             | Pruritus, transaminases, BAs more effectively reduced by UDCA; babies delivered significantly closer to term by patients treated with UDCA |

BAs bile acids; b.i.d twice daily; i.m. intramuscular; i.v. intravenously; LFTs liver function tests; p.o. orally; q.d. once daily; Rx therapy; SAM-e S-adenosyl-l-methionine; UDCA ursodeoxycholic acid
12.1.2.1.6 Global Variations

The prevalence of ICP varies dramatically, the highest being in Chile (4–14%), Bolivia, and Scandinavia (1–2%) [44]; the disease is less prevalent in Europe (0.1–2%), Australia (0.2%), and the United States (<0.1%). Surveys in Bolivia and Chile indicate that ICP is significantly more frequent in certain ethnic groups, such as the Araucanian Indians and another group of South American Indians, the Aimaras.

12.1.3 Specific Dermatoses of Pregnancy

These include only those skin diseases that result directly from the state of gestation or the products of conception [72]. The classification of specific dermatoses of pregnancy into herpes (pemphigoid) gestationis, pruritic urticarial papules and plaques of pregnancy, prurigo gestationis, and pruritic folliculitis of pregnancy, which was proposed by Holmes and Black [30], was subsequently accepted by most authors. A recent reclassification [2] that included ICP and “atopic eruption of pregnancy” (the latter comprising AD, prurigo gestationis, and pruritic folliculitis of pregnancy) in the specific dermatoses of pregnancy was debated [12].

12.1.3.1 Herpes (Pemphigoid) Gestationis

12.1.3.1.1 Etiology and Pathophysiology

Herpes gestationis (HG) is a rare autoimmune bullous dermatosis of pregnancy and puerperium closely related to the pemphigoid group of bullous disorders. The antibody that incites the pathology in HG belongs to the IgG1 subclass and can activate complement through the classical pathway. A recent study [60], however, showed predominance of IgG4 subclass in lesional skin; whether this is related to the stage of the disease or other factors, such as a switch to this specific subclass by the maternal immune system during pregnancy, requires further investigation. The major pathogenic antigen is the bullous pemphigoid 180-kDa hemidesmosomal glycoprotein [56]. Reactivity against both the 180-kDa and 240-kDa bullous pemphigoid antigens is detected in 10% of cases. Serum antibody titers do not correlate with the severity of disease and may remain low positive even after clearance of the eruption. Nevertheless, serum autoantibody levels paralleled disease activity in a recent study that employed ELISA [69]. Autoantibodies recognize the NC16A2 (MCW-1) epitope in the noncollagenous domain (NC16A) of the transmembrane bullous pemphigoid 180-kDa antigen [50]; additionally, other epitopes on the intracellular and/or extracellular domains of the 180-kDa antigen may be also targeted [16]. Epitopes within the NC16A domain relevant for blister formation in HG have been identified [27]. A case of HG with predominantly oral lesions and IgA autoantibodies targeting the C-terminus of 180-kDa antigen was reported [67]; these findings may indicate a broader clinical and immunopathologic spectrum of HG.

Preliminary studies [51] indicated that the autoimmune T lymphocytes express a Th1 cytokine profile. A recent study [21], however, showed a population of Th2 cells in the inflammatory infiltrate in lesional skin and the authors speculated that these cells may be implicated in the very early stages of the autoimmune response. Some authors postulated that an immunologic response occurs against class II placental antigens of paternal haplotype, and the antibody then cross-reacts with a maternal skin basement membrane epitope [38]. An association with human leukocyte antigens (HLA) DR3 (61–80%), DR4 (52%), or both (43–50%), and the C4 null allele has been reported. The role of paternal antigens has been debated. Although a change in paternity has been occasionally associated with the onset of the disease [31], skip pregnancies despite having the same partner occur, which may be due to mother and fetus being fully compatible at the HLA-D locus [31].

12.1.3.1.2 Clinical Characteristics and Diagnosis

HG has been exceptionally associated with choriocarcinoma and molar pregnancy [19]; postpartum HG has
been reported as a paraneoplastic syndrome of choriocarcinoma [17]. In most cases, the course of the cutaneous disease paralleled the course of the tumor. The disease starts most commonly during the second or third trimester (mean onset at 21 weeks) or in the immediate postpartum period (20% of cases). The evolution of the eruption is similar to that of bullous pemphigoid. HG starts in half of the cases with severely pruritic urticarial papules and plaques on the abdomen that commonly involve the umbilicus. A generalized bullous eruption rapidly follows that may affect the palms and soles but rarely the face and mucous membranes (Fig. 12.1.1). Tense bullous lesions arise in both inflamed and clinically normal skin and usually heal without scarring. HG runs a variable clinical course but a flare at the time of delivery is typically seen (75%).

The disease usually subsides spontaneously even without treatment through the weeks to months after parturition, but a protracted course and/or “conversion” to bullous pemphigoid has been exceptionally reported.

Overlapping features of HG and bullous pemphigoid have been reported in some cases [1] and the differentiation between chronic HG and bullous pemphigoid can be difficult. HG often recurs in future pregnancies, usually appearing more severe and earlier in gestation [19]. Skip pregnancies (8%), however, have been reported [31, 35]. The duration of HG postpartum may increase in subsequent pregnancies. Exacerbations during ovulation or the first few menstrual periods after delivery have been reported. Recurrence with oral contraceptives has been documented [31] in as many as half of the patients with a history of HG who subsequently took oral contraceptives. Recurrence typically starts within days to weeks after initiation of oral contraceptive use and disappears after their withdrawal. The effects of nursing practices (breastfeeding vs. bottle-feeding) and prolactin on the postpartum duration of HG have been poorly clarified. The differential diagnosis of HG includes drug eruption, erythema multiforme, allergic contact dermatitis, pruritic papules and plaques of pregnancy (PUPPP, see below), and diseases of the bullous pemphigoid group. PUPPP can manifest itself with urticarial and/or vesiculobullous lesions indistinguishable from those of HG and can be differentiated from HG by direct skin immunofluorescence (negative in PUPPP).

Histopathologic features include a spongiotic epidermis, marked papillary dermal edema, and a mixed mild perivascular lymphohistiocytic infiltrate with many eosinophils. A subepidermal blister develops during the bullous phase of the eruption as a result of necrosis of basal keratinocytes; this type of necrosis is encountered less often in bullous pemphigoid. Direct immunofluorescence of lesional, perilesional, and uninvolved skin shows heavy linear C3 deposition along the basement membrane zone in the vast majority of patients [43]. Salt-split skin testing shows that the antibody binds to the roof of the vesicle. Concomitant immunoglobulin G (IgG) deposition is found in only about 25–30% of patients. IgG is, however, positive (93%) when indirect complement-added immunofluorescence is used [19]. The deposition of IgG1 (historically called herpes gestationis factor) has been found in almost all patients studied with monoclonal antibodies. Linear deposition of C3 and IgG has been demonstrated in the skin of neonates of affected mothers and along the basement membrane zone of amniotic epithelium [19]. Electron microscopy studies show that the deposits of immunoreactants are localized to the upper part of the lamina lucida, just beneath the plasma membrane of basal keratinocytes.

Fig. 12.1.1 | Herpes (pemphigoid) gestationis: urticarial plaques progress into generalized tense bullae on erythematous base. In this rare case, the lesions affected the face (Courtesy Jeffrey Callen, MD)
12.1.3.1.3 General Therapeutic Outline

Oral corticosteroids are required in most cases of HG. Alternative immunosuppressive and other treatments have been attempted in recalcitrant HG with variable results. The pregnant female should be counseled that there is no evidence that any treatment can prevent the fetal risks associated with the disease.

12.1.3.1.4 Current Established Therapies

Most patients with HG respond to oral steroids within a few days. Topical steroids and oral antihistamines can be used in mild cases but rarely control the eruption. Most patients respond to low prednisone doses, 20–40 mg daily in divided doses, although doses as high as 180 mg/day have been used. Once new blister formation has been suppressed, prednisone should be tapered to lower doses (5–10 mg/day) or even discontinued as the pregnancy progresses. The dosage should be increased or therapy resumed at the time of delivery to control the anticipated exacerbation. Postpartum oral steroids at doses of 20 mg/day allow safe breastfeeding. In some cases, HG may persist for months to years after delivery. The serious adverse effects of long-term steroid therapy have prompted a search for alternative treatments. Several cases of recalcitrant HG have been treated with plasmapheresis, immunopheresis, chemical oophorectomy with goserelin, and ritodrine [45, 74]. High-dose intravenously administered immunoglobulin in combination with cyclosporin has shown variable success [26]. Minocycline and nicotinamide have been used anecdotally in one case of postpartum HG. Immunosuppressive and anti-inflammatory agents, such as cyclophosphamide, pyridoxine, gold, methotrexate, or dapsone, has been used postpartum in refractory cases [43, 45, 71]. Nevertheless, these agents have been neither consistently effective nor safe, and their use is limited to non-nursing patients. Early delivery may be considered in troublesome cases, depending on mother’s condition, gestational age, and fetal lung maturity.

12.1.3.1.5 Complications to Avoid

Mother is at increased risk for Graves’ disease, which does not develop simultaneously with HG. Patients often have family histories of autoimmune thyroid disease and pernicious anemia. The increased prevalence of HLA-DR3 and HLA-DR4 alleles among patients with HG, Graves’ disease, and pernicious anemia may explain not only the enhanced genetic predisposition to these disorders but also their frequent coexistence [19]. Once the diagnosis of HG has been established, the pregnancy should be considered to be high risk. An association with small-for-gestational age infants and preterm delivery has been reported [68], but there is no increase in fetal morbidity or mortality with the exception of one case of fetal cerebral hemorrhage. The fetal risks may not decrease with the use of systemic steroids and are thought to be due to low-grade placental insufficiency [19, 45]. A mild neonatal vesiculobullous eruption occurs in 5–10% of cases [36] secondary to

| Table 12.1.2 Specific dermatoses of pregnancy: Summary of management options [59] |
|-----------------------------|---------------------------------------------------------------|
| **Herpes (pemphigoid) gestationis** |
| Topical steroids with an oral antihistamine for early urticarial lesions |
| Oral steroids in most cases |
| Plasmapheresis (1 case) |
| Ritodrine (1 case) |
| Immunoapheresis (1 case) |
| Cyclosporine with intravenous immunoglobulin (1 case) |
| Chemical oophorectomy with goserelin (1 case) |
| Minocycline and nicotinamide postpartum in nonbreastfeeding mother (1 case) |
| Immunosuppressants postpartum in nonbreastfeeding mothers |
| **PUPPP (polymorphic eruption of pregnancy)** |
| Topical steroids and/or antipruritic medications with or without an oral antihistamine |
| Oral steroids in severe cases |
| UVB (anecdotal) |
| **Prurigo of pregnancy** |
| Topical steroids and/or antipruritic medications with or without an oral antihistamine |
| Oral steroids in severe cases |
| **Pruritic folliculitis of pregnancy** |
| Topical benzoyl peroxide |
| Topical steroids |
| Oral antihistamines |
| Narrow band UVB (1 case) |
passive transplacental transfer of HG antibody and typically resolves spontaneously in a few weeks as the maternal antibodies clear from the infant’s blood. Nevertheless, the duration of lesions is variable, and because the immune system of the infant is still developing, there is a significant risk of skin infection that may become systemic. Monitoring the infant for adrenal insufficiency is required for infants of mothers treated with long courses of systemic steroids.

**Take Home Message**

- Positive direct immunofluorescence testing is the hallmark of HG. Systemic steroids is first-line treatment for HG. The fetal risks associated with the disease seem less severe than previously thought.

### 12.1.3.1.6 Global Variations

The prevalence of HG is estimated between 1 in 10,000 and 1 in 50,000 pregnancies, and the disease is most common among white patients.

### 12.1.3.2 Pruritic Urticarial Papules and Plaques of Pregnancy (PUPPP)

#### 12.1.3.2.1 Etiology and Pathophysiology

The pathogenesis of PUPPP (or “polymorphic eruption of pregnancy”) has not been established. Immunohistologic studies have not provided us with conclusive results, which is probably due to the fact that hormonal changes during pregnancy may modulate and alter cytokine production, and among others induce a switch from Th1 to Th2 profile at the maternal–fetal interface that may be involved in the maintenance of successful pregnancy [21]. A preliminary study showed an infiltrate of T helper lymphocytes, activated T cells in the dermis, dermal dendritic cells, and epidermal Langerhans cells in lesional skin in PUPPP patients [8]. This profile as well as the strong HLA-DR expression suggests an activation of the skin immune system to an unknown antigen. Compared to the immunohistologic profile of HG, PUPPP shows a stronger expression of HLA-DR by a wider spectrum of cells, including keratinocytes, and the T cells seem to express a more heterogeneous profile as they are able to secrete Th1- and Th2-like cytokines [21].

It has been postulated that rapid abdominal wall distention in primigravidas during the late months of pregnancy may lead to damage of the connective tissue of the abdominal skin and thus trigger an inflammatory process [11, 18]; this has been supported by the localization of lesions to abdominal striae and associations with multiple gestation pregnancy [45], abnormal weight gains in the mother and fetus, and maternal obesity [58]. A meta-analysis [45] that revealed a tenfold higher prevalence of multiple gestation pregnancy in female patients with PUPPP supports this hypothesis. Multiple gestation pregnancy is associated with higher estrogen/ progesterone levels, and progesterone has been shown to aggravate the inflammatory process at the tissue level, possibly through the expression of progesterone receptors by keratinocytes. Interestingly, increased progesterone receptor levels have been detected in skin lesions of PUPPP [34]. A high frequency of atopy (55%) was reported in a recent study [64] but has not been corroborated by other studies; the authors reported also an IgE elevation in PUPPP (28%) and other dermatoses of pregnancy but the significance and specificity of mild IgE elevations in pregnancy have been debated [12]. Finally, a small preliminary study showed fetal DNA in skin lesions of PUPPP; the authors suggested that it can result from fetal cell migration to maternal skin secondary to peripheral blood chimerism [3]. Additional data is required to clarify if microchimerism could be involved in the pathogenesis of PUPPP.

#### 12.1.3.2.2 Clinical Characteristics and Diagnosis

PUPPP is the most common specific dermatosis of pregnancy. This severely pruritic inflammatory skin disorder occurs typically in primigravidas in the third trimester (mean onset at 35 weeks) and rarely postpartum [4, 49]. It has been associated with a predominance
of male infants (55%) [64, 72]. The most commonly affected sites are the abdomen and proximal thighs. The lesions start in the abdominal striae in two-thirds of the cases, and typically show periumbilical sparing (Fig. 12.1.2) [43, 45].

The eruption is polymorphous, showing urticarial and occasionally vesicular, purpuric, polycyclic, or targetoid lesions [4]. Excoriations and eczematous features are common at later stages. Lesions can spread over the trunk and extremities but usually spare palms and soles. Involvement of the face and dyshidrosis-like lesions on the extremities are unusual. Generalized PUPPP may resemble a toxic erythema or AD. PUPPP resolves spontaneously or with delivery.

Skin histopathology shows spongiotic dermatitis and a perivascular or upper dermal lymphohistiocytic infiltrate with variable numbers of eosinophils [43]; eosinophil infiltration is more extensive in HG than PUPPP. Epidermal changes, such as parakeratosis, acanthosis, and exocytosis, can be seen and are more prominent in older lesions and those with polymorphous morphology, thus reflecting the clinical evolution of the lesions [32, 64]. Serology is negative; a decrease in serum cortisol in one study [72] has not been corroborated by other studies. Direct immunofluorescence is negative, which helps differentiate the disease from HG. PUPPP should also be differentiated from ICP and specific dermatoses of pregnancy such as prurigo of pregnancy and pruritic folliculitis of pregnancy, hypersensitivity reactions, viral exanthems, and drug eruptions.

### 12.1.3.2.3 General Therapeutic Outline

Topical treatment for symptomatic relief with or without an oral antihistamine is usually required. The pregnant female needs to be counseled that the disease has not been historically associated with any substantial fetal risks.

### 12.1.3.2.4 Current Established Therapies

Mild PUPPP can be treated with antipruritic topical medications, topical steroids, and oral antihistamines. In cases of severe itching or when the lesions are very extensive, a short course of oral prednisone may be necessary and appears to have no adverse effects on the pregnancy. The risk of fetal adrenal suppression secondary to a short course of oral steroid is very low as shown by the fact that the maternal–fetal gradient of prednisolone is 10:1 [23]. UVB has been used anecdotally with some success [45].

### 12.1.3.2.5 Complications to Avoid

The perinatal outcome in most studies has been comparable to pregnancies without PUPPP. The fetal prognosis has been invariably favorable, with fetal deaths being extremely uncommon [54, 72]. A recent study [58], however, indicated an association with hypertensive disorders, but there is no other evidence in the literature regarding this association. In the same study, higher rates of labor induction and subsequent cesarean section were noted in the PUPPP group but in multivariate analysis PUPPP was not an independent risk factor for cesarean delivery. Further studies are required to investigate these associations.

---

**Take Home Message**

> PUPPP is the most common specific pregnancy dermatosis and affects primarily primigravida during the third trimester of gestation. The disorder has been associated with multiple gestation pregnancy, but most studies have shown no substantial maternal or fetal risks.
12.1.3.2.6 Global Variations

PUPPP affects between 1 in 130 and 1 in 300 pregnancies. It has been primarily reported in Caucasian females, and its prevalence in other ethnic groups seems to be lower.

12.1.3.3 Prurigo of Pregnancy

12.1.3.3.1 Etiology and Pathophysiology

Prurigo of pregnancy (PP) has been associated with a family history of ICP [62]. It has been speculated [72] that PP and ICP are closely related conditions, being distinguished only by the absence of primary lesions in ICP, and may be different levels of severity of the same entity [7]. Other authors [72] reported an association with personal or family history of AD and elevation of serum IgE (4 out of 12 patients; no control group), and suggested that PP may be the result of pruritus gravidarum in women with an atopic diathesis. In the most recent study of the group [2], it was suggested that PP is not a distinct entity but should be included in the spectrum of “atopic eruption of pregnancy,” although 4 out of 49 PP patients in the study fulfilled only minor criteria of atopy. Nevertheless, a significant percentage of PP patients never had eczema or a well-documented atopic background [45, 72]. The association with atopy has not been confirmed by other studies, and the importance of mild IgE elevations in pregnancy was debated [12] as maternal serum IgE levels in gestation can be affected by ethnic, genetic, and psychosocial factors [52].

although lesions may rarely persist for up to 3 months. Recurrence with subsequent pregnancies is variable. PP shows nonspecific histopathologic features and skin immunofluorescence is negative. Serologic tests may show elevated IgE levels [72]. The differential diagnosis of PP includes pruritic dermatoses unrelated to pregnancy, other specific dermatoses of pregnancy, ICP, drug eruptions, arthropod bites, and infestations such as scabies.

12.1.3.3.3 General Therapeutic Outline

Topical treatment for symptomatic relief is usually required. The pregnant female needs to be counseled that in recent large studies the disease has not been associated with fetal risks.

12.1.3.3.4 Current Established Therapies

PP is treated symptomatically with moderately potent topical steroids, if necessary intralesional or under occlusion, and oral antihistamines [32]. A short course of oral steroid is rarely necessary.

12.1.3.3.5 Complications to Avoid

Early reports [70] of a dismal fetal outcome in patients with PP have not been confirmed by.
subsequent studies. The birth weight is normal, and there is a consensus that the pregnancy outcome is favorable. The disease has not been associated with any maternal risks.

**12.1.3.3.6 Global Variations**

PP affects approximately 1 in 300 to 1 in 450 pregnancies. There is insufficient data on the incidence of PP in non-Caucasian females.

**12.1.3.4 Pruritic Folliculitis of Pregnancy**

**12.1.3.4.1 Etiology and Pathophysiology**

The etiology of pruritic folliculitis of pregnancy (PFP) remains unclear. Increased serum androgen levels [75] or association with ICP [20] have been reported in PFP but were most likely coincidental. It has been postulated [75] that PFP may be a form of hormonally induced acne, based on clinical similarities with steroid acne. Nevertheless, a comedonal component, typically seen in steroid acne, is absent in PFP. Other authors [62] have suggested that PFP can be a variant of PUPPP based on rare reports of follicular lesions in some PUPPP patients. Yet, the clinical and histopathologic features of PFP differ from those of PUPPP. A recent study included a case of PFP in the spectrum of “atopic eruption of pregnancy” on the basis of a history of childhood eczema in the patient and family history of atopy. Nevertheless, none of the 32 PFP cases that have been reported have been associated with atopy. Another hypothesis that PFP can be caused by *pityrosporum* was debated [46].

**12.1.3.4.2 Clinical Characteristics and Diagnosis**

PFP is a rare specific dermatosis of pregnancy. PFP was first described by Zoberman and Farmer who reported a mildly pruritic generalized eruption in six pregnant women that develop between the fourth and ninth month of gestation and resolved spontaneously at delivery or postpartum [76]. Since the original description, 26 cases have been reported. Underreporting is probably common because it can be easily mistaken for microbial folliculitis or acne. PFP presents with sparse pruritic follicular erythematous papules and pustules that affect primarily the trunk (Fig. 12.1.4); the lesions often have an acneiform appearance [42]. The eruption resolves spontaneously at delivery or postpartum and may recur in subsequent pregnancies [76]. The histopathology is that of sterile folliculitis, and special stains for microorganisms are invariably negative. Skin immunofluorescence and serology are negative. The differential diagnosis of PFP includes an infectious folliculitis and specific dermatoses of pregnancy. Stains for microorganisms and cultures from the pustular lesions can exclude microbial folliculitides.

**12.1.3.4.3 General Therapeutic Outline**

PFP is treated primarily with topical medications, and occasionally with oral antihistamines for symptomatic relief. The pregnant female should be advised that PFP resolves spontaneously postpartum and has not been associated with any fetal risks.
12.1.3.4.4 Current Established Therapies

PFP has been treated with topical steroids, benzoyl peroxide, and narrow band UVB [43]; relief of pruritus has been reported with oral antihistamines.

12.1.3.4.5 Complications to Avoid

PFP was associated with a decreased birth weight and a male to female ratio of 2:1 in the largest series of patients [72]. Preterm delivery was reported in one case but no other maternal or fetal risks.

Take Home Message

> PFP is a rare, ill-defined, specific dermatosis of pregnancy that has not been associated with any fetal risks. The etiology of the disease remains elusive, and its status as a distinct entity has been debated.

12.1.3.4.6 Global Variations

Because of the rarity of the condition (approximately 30 cases reported), differences among ethnic groups have not been reported.

References

12.2.1 Pediatric Dermatology Therapy: Scope, Specific Challenges, and Worldwide Variations/Priorities

Skin disorders affecting children are very varied, but the bulk of pediatric dermatology can be summarized easily. In the newborn, many transient rashes correspond to the adaptation of skin to its new atmospheric milieu, and need mostly a diagnostic and reassurance [1]. However, some of the most severe – but rare in western countries – inherited skin disorders such as congenital ichthyoses and epidermolysis bullosa (EB) manifest dramatic features at birth, and need very specialized skills for their initial management and later a well-coordinated program at a specialized center for therapy, genetic counseling, and prenatal diagnosis (Chap. 10). In infants, inflammatory skin disorders are largely dominated by atopic dermatitis which affects up to one-fourth of infants in some countries. The management of atopic dermatitis is frequently considered controversial, because of controversy regarding its pathophysiology and especially the persistence of allergy as a unifying concept, but there is an emerging consensus to consider atopic dermatitis primarily as a skin disorder and skin as a primary target for prevention and treatment [2, 3]. The most common tumor in infancy is the infantile hemangioma (IH), which affects 5–10% of children, with an increased prevalence in premature infants (see Sect. 12.2.3.3). Common infectious disorders include acute viral rashes and more chronic viral infections such as verruca vulgaris and molluscum contagiosum (Chap. 2.3), tinea capitis (Chap. 2.2), and pyoderma (Chap. 2.1). A large burden of severe pyoderma is currently linked to complications of chickenpox with both topical abscesses/cellulitis and toxinc manifestations [4]. When compared to adults, reactions to systemic drugs are rare and simpler to diagnose because the number of drugs is usually limited in a usually healthy child. On the contrary, a common problem in hospital practice is to make a differential diagnosis in a child treated for leukemia between early graft versus host disease and a drug reaction. Systemic reactions to topical drugs are more common in premature newborn due to more permeable skin barrier and higher skin surface to weight ratio [5]. Drugs to exclude...
topically in priority include aniline dye, neomycin, alcohol-based solutions/creams, hexachlorophene, and iodine (Table 12.2.1). Adult-type common skin disorders, such as psoriasis, vitiligo, lupus erythematosus, and rosacea [6], have usually, relative to common adult onset cases, a more inherited background and also a more severe presentation and course. It is not currently well established that an early and vigorous intervention is helpful modifying the course of chronic skin disorders; but an interesting hypothesis is that in some inflammatory disorders the autoreactive component (auto-inflammation) can be limited by such an approach. Thus a wait-and-see position, commonly held in children, is usually not tenable when an efficient treatment is at hand at a reasonable benefit-to-risk ratio, for example, in the case of atopic dermatitis [7]. A problem which is specific to the vulnerability of the child and applies particularly to pediatric dermatology is the need to consider child abuse and neglect in some circumstances, such as in difficult-to-classify dermatoses including burns and purpura, specific infectious diseases in particular locations (e.g., perianal condylomas, see Sect. 12.2.3.4). Lastly, due to the rapid improvement of knowledge in the field of genodermatoses, early diagnosis is important to implement efficient substitution, cell or gene therapy [8].

There are at the world level major differences in the epidemiology of pediatric skin disorders that affect priorities and choices for therapy. Developing countries are often faced with infections and infestations, and scabies is a public health priority [9]. Patients with greater pigmentation more readily manifest hypopigmentation,
especially vitiligo: in this setting, cosmetic disfigurement may justify early and more aggressive interventions, including surgical techniques. Vascular birthmarks and pigmented nevi are more conspicuous in white skin, and this influences management of these conditions. High consanguinity is common in Maghreb, Middle-East, and Indian-Pakistanis families and severe autosomal recessive genodermatoses such as epidermolysis bullosa ichthyosis and xeroderma pigmentosum are more common, which poses specific problems, including genetic counseling, prenatal diagnosis, or better preimplantation genetic diagnosis when feasible. However, the development of new techniques of cell or gene therapy using the recent knowledge on bone-marrow-derived stem cells that repopulate the skin may help in the future those affected with the severe forms of this group of monogenic skin disorders [10]. Public health priorities in pediatric dermatology must take into account epidemiologic, demographic, and cultural contexts. In western countries, with a majority of low phototype individuals, prevention of sunburn in infants and young children is a key issue in pediatric dermatology. Similarly, the epidemics of allergic disorders that has its primary root in skin barrier impairment was until recently neglected. A new field of skin-based prevention is widely opened, which may prove useful to address these epidemics [11, 12].

12.2.2 Highlights of Some Important Disorders in Pediatric Dermatology

We have selected in this section some important diagnoses that are frequently missed and need urgent or specific treatments in pediatric dermatology.

12.2.2.1 Scabies

**Key Features**

- Misdiagnosis and treatment with topical corticosteroids is common in young children (Fig. 12.2.1).
- All contact individuals need to be treated simultaneously

Fig. 12.2.1 Crusted (Norwegian) scabies treated successfully with a combination benzoyl benzoate 10% solution plus ivermectin [13]

12.2.2.1.1 Etiology and Pathophysiology

(See Chap. ELSTON)

12.2.2.1.2 Clinical Characteristics and Diagnosis

The child with pruritus is usually considered first as having atopic dermatitis. This explains common errors in disease management in this age group. Treatment of scabies with topical corticosteroids may lead to the clinical presentation of crusted (Norwegian) scabies [13], which disseminate further the disease to the community in a short period of time. The history is similar to that of adults: (1) shared pruritus between closely related individuals, especially within families, (2) increased pruritus at night when there is an increased motility of mites, and (3) furrows and vesicles/papules with eggs, nymphs, or adult mites at scrapings. Differences in lesional distribution occur in infants with a predilection of sole and axillary lesions. Clearly the most important is to consider scabies whenever a pruritic condition is present,
whatever the age group. Scabies may start very soon after birth; some cases have been diagnosed at 2 or 3 weeks of age in our department.

### 12.2.2.3 General Therapeutic Outline

The treatment in children is similar to that of adults.

### 12.2.2.4 Current Established Therapies

The management of scabies in infants has been debated because of the systemic risks of topical treatments: in countries where the drug is available, permethrin 5% in cream has a good safety profile and should be used first [14]. In our country, we have used over the last 25 years the benzyl benzoate 10% solution in one application of 24 h on the whole body including the face in infants without noticing side effects and with a good efficacy in monotherapy.

### 12.2.2.5 Experimental Approaches

The use of ivermectin in infants and children with scabies is not yet recommended but may be useful in case of disseminated of crusted scabies in addition to the first-line topical scabicide [13].

### 12.2.2.6 Complications to Avoid

It is mandatory to follow the other recommendations relative to contact persons to avoid recontamination [14].

### 12.2.2.7 Global Variations

Permethrin is used in the USA. Scabies is epidemic in several countries especially sub-Saharan Africa.

### 12.2.2.2 Kawasaki Disease

#### Key Features

- Kawasaki disease (KD) is the most common systemic inflammatory disease in pediatric hospital practice (Fig. 12.2.2)
- Early diagnosis and treatment prevents cardiovascular complications.

#### 12.2.2.1 Etiology and Pathophysiology

Autoimmunity appears to be a key component in the pathogenesis of arterial damage in KD but the triggering event(s) are still not known. The potential role of

---

**Fig. 12.2.2** Typical Kawasaki disease case showing rash, palmar involvement, and cheilitis

---

**Take Home Message**

- Do not forget scabies when evaluating an itchy rash in a child or an infant
bacterial agents acting as superantigens and triggering massive activation of the immune system in genetically predisposed children is a current area of research focus.

12.2.2.2 Clinical Characteristics and Diagnosis

Kawasaki disease (KD) is an acute systemic vasculitis that predominantly affects children younger than 5 years of age, with an incidence of 10–15 per 100,000 children in the United States and about 150 per 100,000 in Japanese children. It is now considered as the predominant cause of acquired heart disease in children living in developed countries, with coronary artery aneurysms or ectasia occurring in about 25% of untreated patients. KD is characterized by a wide variety of clinical features. Some of them are considered as diagnostic criteria for typical forms of KD: prolonged fever for at least 5 days, and four of the following criteria: (1) bilateral most often non-purulent conjunctival injection, (2) erythema of the hands and feet that precede peeling of the fingers and toes, (3) pharyngitis with strawberry tongue and red and fissured lips, (4) maculopapular or scarlatiniform or urticarial (polymorphous) rash, and (5) asymmetric cervical lymphadenopathy [15]. ECG anomalies or early ultrasound anomalies such as pericardial effusion or coronary dilation are of diagnostic importance. Since there is no specific biomarker, other findings can be helpful to support the diagnosis of KD, including severe asthenia, early perineal desquamation, erythema at a BCG vaccination site, anterior uveitis, together with laboratory findings such as elevated erythrocyte sedimentation rate and C-reactive protein, and elevated platelet counts. Atypical forms of KD include incomplete forms especially in children younger than 1 year, atypical rashes mimicking erythema multiforme or scarlet fever, and patients with preponderant gastrointestinal tract or central nervous system involvement.

12.2.2.3 General Therapeutic Outline

Prompt treatment is essential to decrease the risk of coronary artery abnormalities (from 25 to 35 to about 5% of patients). Following guidelines proposed by the American Heart Association [16] and the Cochrane Database Systematic Reviews [17, 18], acute management of Kawasaki disease should include intravenous immunoglobulin (IVIG) and high-dose aspirin.

12.2.2.4 Current Established Therapies

The recommended therapy during the acute stage of KD should be given within 10 days of onset of fever and consists of a combination of one single infusion of IVIG, 2 g/kg over 4–12 h, and oral aspirin at 80 mg/kg/day in four equally divided doses. Fever remits usually 24–36 h after initiation of the treatment, with improvement of the general health and progressive disappearance of the skin rash. Follow-up echocardiograms should be performed by a trained physician at 2 weeks and 2–3 months after initial treatment, or more frequently in doubtful cases. The high-dose aspirin is given until the child is afebrile and then reduced to an antithrombotic effect-dose of 3–5 mg/kg as a single daily dose for at least 2 months. During the following months, administration of live virus vaccines should be delayed to avoid an ineffective immunization related to the presence of passively acquired antibodies (IVIG).

About 10% of patients fail to respond to initial treatment with IVIG, with recurrence of the fever or persistent fever beyond 24–48 h after completion of the first infusion. A second course of IVIG is then effective in 75% of cases.

12.2.2.5 Experimental Approaches

In the remaining cases of IVIG-resistant KD, patients may respond to one or two courses of intravenous corticosteroid therapy (prednisolone 1–2 mg/kg/day for 3 days) or infliximab [19]. Moreover, recent studies have shown that corticosteroids, given in addition to IVIG therapy [20], could be an effective adjuvant therapy in the initial treatment of KD, but further studies are required before we may recommend this combination for the management of all patients with KD.

12.2.2.6 Complications to Avoid

Diagnosis delay causes morbidity and mortality. Thus it is probably necessary to overdiagnose some cases such as for appendicitis to avoid complications.
**Global Variations**

Kawasaki disease is more prevalent in Japan but also in Asian and black-skin background individuals in western countries.

**Alarming Hemangiomas**

### Etiology and Pathophysiology

Infantile hemangiomas (IH) are the most frequent benign tumors in young children, and no therapy is necessary in most cases. Their pathophysiology is still poorly understood, but there is evidence of an impaired regulation of the angiogenic program in the first weeks of life at the period of maximal growth of skin and other tissues. A transient dysregulation of the transcription factor HIF1 alpha pathway is hypothesized.

### Clinical Characteristics and Diagnosis

Four clinical presentations may be distinguished: (1) high risk localization, including lesions of the upper airway – particularly in IH with a beard distribution [21] – periocular IH, and hepatic location, (2) lesions with a predictably severe cosmetic result, including widespread IH of the face and the so-called Cyrano hemangioma, (3) complications, particularly large ulcerations, and (4) segmental IH, i.e., PHACES syndrome and lumbosacral hemangiomas (SACRAL syndrome) [22]. The Kasabach-Merritt syndrome, which arises in vascular malformations distinct from hemangiomas, will not be discussed here.

### General Therapeutic Outline

Systemic corticosteroids are the first-line therapy for alarming hemangiomas, even though our knowledge about their mechanism of action is poor [23]. Due to their potential adverse effects, a careful monitoring of children receiving high dose of prolonged corticosteroid therapy is required.

### Current Established Therapies

In early stages of extensive IH, oral corticosteroid treatment (prednisone or prednisolone) is commonly used at an initial daily dose of 2–3 mg/kg. In nonresponsive patients, the daily dose may be increased to 5 mg/kg. Blood pressure monitoring and echocardiogram are recommended before the onset of therapy, followed by repeated physical examination and blood pressure measurement twice monthly [26]. To avoid overestimation of blood pressure, physicians who are not trained with pediatric patients should use an age-adapted...
12.2.2.3.5 Experimental Therapies

As a second-line therapy for corticosteroid-resistant IH, vincristine or interferon-alpha may induce early regression, but their favorable effects have been shown only in case reports or limited open studies [27, 28]. Excisional surgery is widely used in the management of significant residual damage. Some recent series also found good results in early IH, leading to recommendation for early surgery in nasal-tip and large periocular IH and in refractory large ulcerated lesions [29]. More recently, we have proposed as a first-line therapy propranolol following a serendipitous observation, and the results appear to be promising [30]. Propranolol is now in most centers the first line treatment for severe IH.

12.2.2.3.6 Complications to Avoid

Those are due to the systemic or topical administration of corticosteroids. For systemic steroids, cardiovascular monitoring is necessary with cardiac ultrasound especially if dosages of more than 2 mg/kg/day are envisaged because of steroid induced cardiomyopathy. For topical treatments, intravascular injections have caused complications especially in hemangiomas situated around the orbit and treated with oily preparations, which can cause a thrombosis of the draining ophthalmic vein and blindness.

Take Home Message

- Early evaluation and aggressive multidisciplinary management is useful in a subset of cases to identify early complications

12.2.2.3.7 Global Variations

None known

12.2.2.4 Condylomata Acuminata

12.2.2.4.1 Etiology and Pathophysiology

Human papilloma viruses cause the disease. In adults, genital warts affect about 1% of the general population and are exclusively associated with sexual transmission. In contrast, genital warts are less prevalent in children, and modes of transmission include perinatal transmission, auto-inoculation from verruca vulgaris, “innocent” hetero-inoculation from parental HPV lesions, and sexual abuse [31].

12.2.2.4.2 Clinical Characteristics and Diagnosis

In the genital area, children have more frequently papular lesions than classic verrucous exophytic warts. Lesions are located in the perianal area in about two-third of cases, usually without mucosal involvement, and affect the anogenital area in about one third of cases. Isolated involvement of the genital area is rare. Diagnosis...

Key Features

- The diagnosis of child abuse is a crucial challenge because there is no definitive clinical feature or laboratory test (Fig. 12.2.4).

Fig. 12.2.4 Perianal condyloma in a male infant. Maternal transmission
is clinical, but HPV genotyping is used to help in establishing diagnosis and route of transmission.

12.2.2.4.3 General Therapeutic Outline

The management of genital warts in children requires a dual approach that includes (1) investigation of the mode of infection and (2) specific treatment to remove the warts.

12.2.2.4.4 Current Established Therapies

Assessment of children should be multidisciplinary, and sexual abuse should be considered critically and comprehensively including the following criteria: age at onset, presence of warts in other locations in the child, HPV lesions in the parents, physical examination searching for sign of sexual abuse or of battered child syndrome, assessment of the social and familial background, HPV type, and microbiologic workup for other sexually transmitted infections [32]. In our experience, a systematic psychological investigation – including interview and projective tests – can shed light on the mode of transmission.

Several therapeutic options exist. No treatment may be considered in minor forms, knowing that spontaneous disappearance may occur within 5 years in about half of the cases [33]. Surgical excision plus electrocautery under general anesthesia is useful because it gives rapid healing, with minor clinical recurrences in 20–30% of the cases, and allows practicing a non-traumatic genital examination at the same time [34]. Ablation using carbon dioxide laser seems to give similar results.

12.2.2.4.5 Experimental Therapies

Pulsed dye laser has been shown to be an effective treatment in adults but has been reported in children only in isolated case reports. Medical therapies, i.e., imiquimod and podophyllotoxin, may be used particularly as adjuvant treatments or in cases of recurrence after surgical or laser removal [35]. Imiquimod is used as 5% imiquimod cream applied to the child every other day for 1–3 months, and podophyllotoxin 0.5% gel is usually applied daily for 3 consecutive days followed by a 4-day treatment-free period, and repeated until clearance. HPV vaccination as used in prepupertal females may decrease the burden of HPV infection in children in the future.

12.2.2.4.6 Complications to Avoid

There are two major complications in this field, either under-suspicion of or over-suspicion of abuse, and both are problematic. A multidisciplinary approach is essential but does not eliminate mistakes.

12.2.2.4.7 Global Variations

Not clearly currently delineated, but may follow prevalence of genital HPV infection in the population and subject to changes with current prevention campaigns

12.2.2.5 Langerhans Cell Histiocytosis

The cellular origin of some histiocytoses can be based on cell ontogeny:

- CD34+ progenitors mature into CD14+ and CD14- histiocytes.
- CD14- cells further differentiate into LCs.
- CD14+ cells differentiate into either dermal dendrocytes or monocyte/macrophages under the influence of the local microenvironment.

12.2.2.5.1 Etiology

Since the classification of histiocytic disorders by the Writing Group of the Histiocyte Society into three different classes: Langerhans cell histiocytosis (LCH)
(class I), non-Langerhans cell (LC) histiocytoses (class II), and malignant histiocytoses (class III) revisions have been suggested in the light of new developments in the characterization of the central cell type involved in each disorder [36]. LCs occupy a central role in LCH, dermal dendrocytes in juvenile xanthogranuloma, and macrophages in hemophagocytic lymphohistiocytosis [37].

12.2.2.5.2 Clinical Characteristics and Diagnosis

The clinical presentation of LCH is generally that of a papulo purpuric rash of seborrheic distribution in an infant. However, several variants exist and the borders between spontaneous involutive forms found in neonates (Hashimoto-Pritzker variant) and classic LCH are sometimes difficult to define, especially for lesions that begin with a tumor-like appearance. Some cases are triggered by vaccination and lesions are maximal at vaccination sites (Fig. 12.2.5). The major differential diagnosis due to age-related prevalence, as already noted for scabies, is atopic dermatitis, but seborrheic dermatitis is also a consideration. LCH is usually not pruritic but skin lesions may improve with topical corticosteroids. It is important to perform a thorough clinical examination in this setting, because it is sometimes possible to make the diagnosis clinically based on mucosal lesions, or based on bony skull defects, or splenomegaly. In any case, a skin biopsy will be diagnostic.

12.2.2.5.3 General Therapeutic Outline

Treatment options will depend on the stage of the disease, and there is still no consensus as to optimal management of mild disease. Indeed there appears to be more evidence supporting a clonal rather than full-blown malignant nature of this proliferative disorder, leading to nonaggressive management [37]. A multidisciplinary approach is obviously needed given the systemic nature of this disease and enigmatic natural course of some cases. Recurrence is quite common, even in patients treated with multi-agent chemotherapy.

12.2.2.5.4 Current Established Therapies

In the LCHI study, 24 weeks of vinblastine/prednisone treatment gave similar results to an etoposide/prednisone regimen [38]. Fifty-eight percent of cases in each arm experienced at least one recurrence. The DAL-HX 83/90 studies extended treatment to 1 year with more extensive maintenance, resulting in a lower recurrence rate of 32% [39]. An early response at 6 weeks of therapy in LCH I study led to a 94% probability of survival at 3 years, whereas the rate in nonresponders was 34% [37]. A high frequency of the late effects of LCH, 71% in multi-system and 24% in single-system cases, stresses the complicated nature of this disorder and disputes the self-resolving benign course in the majority of cases [40].

12.2.2.5.5 Experimental Therapies

Multicenter trials are currently assessing better approaches.
12.2.2.5.6 Complications to Avoid

It is necessary to avoid drug-related complications, especially in mild disease. Late effects of LCH and its treatment can occur in 50% of cases, diabetes insipidus in 24%, and neurologic problems in 11%. Neurodegenerative changes are the second most frequent central nervous system involvement pattern, commonly involving the cerebellum and basal ganglia in the form of bilateral symmetric lesions. This complication is immunopathologically similar to that of paraneoplastic encephalitis [37].

Take Home Message

- This disorder is easy to diagnose if skin lesions are present by skin biopsy.
- Its management is multidisciplinary, and overtreatment should be avoided due to the nonmalignant course of the disease in most instances.

12.2.2.5.7 Global Variations

Not known

12.2.3 General Therapeutic Principles in Pediatric Dermatology

12.2.3.1 Age Versus Severity in Therapy of Skin Disorders

There is a general tendency among dermatologists not familiar with the principles of pediatrics to undertreat children with the erroneous assumption that therapeutic intervention must be delayed to limit the risks of drugs, and when treating, to use inappropriately low dosages for children, neglecting the fact that on a mg/kg basis, appropriate pediatric drug regimens are generally 1.2–2 times higher than those of adults. Indeed, young children cannot express themselves like adults and demand treatment. Consider some examples: the child with severe atopic dermatitis who cannot sleep properly performs badly at school, and lives overall miserably. If an appropriate severity-based approach is implemented, this will lead to a spectacular recovery of school performances and the child catches up rapidly a normal growth pattern with a recovery of personal well-being. A child with severe ichthyosis can be improved by systemic retinoids introduced early on if required by disease severity and long-term studies have not shown major side effects [41]. A child born with a disfiguring facial birthmark may be left untreated until he experiences the consequences of stigmatization, usually around 5–6 years of age. Early intervention, using surgery or laser treatments (e.g., port wine stains), can be highly beneficial to the child. This kind of consideration applies also to acquired hypopigmented disorders such as vitiligo which may require more aggressive management to limit the progression of the disease [42].

In those times of widespread available information on the internet, it is necessary to handle firmly the management of some difficult situations. The parents with a first born child affected with a severe skin disorder, such as epidermolysis bullosa (EB), ichthyosis, or giant nevus, need to receive a timely and appropriate information. Prognosis is in some instances difficult, especially in case of congenital EB, and communication should be prudent before the results of diagnostic tests, and even after (some rare cases of functional EB may turn out to be benign). If the prognosis is unclear, the family should be told that the future outcome cannot be predicted with certainty. If the family has already obtained internet information, it may be prudent to discuss the issues that have been raised. In any case, a management plan, adapted to each situation, should be proposed and discussed with the parents. For example, for a child born with a disfiguring port-wine stain or giant congenital nevus an agenda for treatment should at best be discussed with the physician-in-charge (laser therapist or surgeon) as quickly as possible to minimize unrealistic expectations and on the other hand to bring accurate information on some more encouraging perspectives (such as cutaneous expansion to remove large skin defects).
Pediatric skin disorders require specialized management, which cannot be delivered optimally without pediatric facilities, including trained nurses, surgeons, radiologists, and anesthetists, not to mention pediatric dermatologists. For example, pain management has improved considerably over the two last decades, based on a better general approach of dedicated staff to limit the consequences of a frightening environment for the affected child and allowing to keep him in close contact with his parents, and by the use of better ambulatory anesthetic techniques such as EMLA (lidocaine-prilocaine) cream and inhaled nitrous oxide analgesia. For example, EB needs a very well trained nursing staff to transfer efficiently the technology of dressings for EB neonates/infants to the parents or other nursing staff closer to the family’s home.

**General Take Home Messages**

- It is crucial to avoid undertreatment of common conditions in childhood, especially in inflammatory skin disorders such as atopic dermatitis and psoriasis, but also in vitiligo where early intervention is helpful before a definitive loss of skin melanocytes. The reasons for undertreatment of skin disorders in children are not always clear, but the reluctance to treat because of age first, assuming that children are less hardy than adults, or because of interference with growth and development, is usually not scientifically founded. It is important to remember that growth/development is usually more stunted by disease than by treatment. Do not forget that parents may also not adhere to the management plans due to personal beliefs or neglect. In extreme cases, if the child is severely affected by this undertreatment by the parents, this could be a strong case for asking for judicial and/or social service intervention. In contrast, aggressive parents seeking to have a “perfect child”, may push the physician to intervene because of a minor cosmetic disfigurement (e.g., infantile hemangioma). The dictum “primum non nocere” should always be kept in mind. Overtreatment of benign and spontaneously remitting cutaneous conditions is a difficult problem, but physicians must be persuasive, and parent’s management through good quality information is a key issue. A step beyond is the syndrome of Munchausen by proxy (fabricated and induced illnesses by the parents), which should be considered in case of equivocal presentation of skin diseases in children [43]. Eventually, it is important to know your limits, and do not hesitate to take the advice of a colleague with more experience than you in pediatric dermatology.

References

12.3.1 Etiology and Pathophysiology of Skin Aging

Skin aging is the accumulation of cellular and structural damage that progressively occurs as individuals get older. The aging process is genetically determined and environmentally modulated. Due to its physical exposure to the environment, skin is particularly susceptible not only to damage from xenobiotics (drugs, chemicals, atmospheric pollution, cigarette smoke), but also to UV irradiation from the sun. On areas of the body that are less covered by clothing (i.e., face, nape of the neck, hands and forearms), photoaging...
and natural aging superimpose, leading to more pronounced alterations in the appearance of the skin.

12.3.1.1 Reactive Oxygen Species Initiate the Aging Process

Oxidative stress is a primary driving force of the aging process. The free radical theory of aging [28] describes the accumulation of damage by reactive oxygen species (ROS) over a lifetime as a result of aerobic metabolism, combined with a decline in antioxidant defenses. ROS include oxygen free radicals (such as superoxide anion \( \text{O}_2^- \), nitric oxide \([\text{NO}^-]\), and hydroxyl radical \([\text{HO}^-]\)) as well as oxygen-containing molecules that facilitate free-radical formation (hydrogen peroxide \([\text{H}_2\text{O}_2]\), hypochlorite \([\text{OCl}^-]\), peroxynitrite \([\text{ONOO}^-]\)). ROS attack nucleic acids, amino acid side chains in proteins, and double-bonds in unsaturated fatty acids, with the hydroxyl radical being the most highly reactive.

Both UVA (320–400 nm) and UVB (290–320 nm) generate ROS in skin cells [31]. ROS are produced by energy transfer from UV irradiation-absorbing chromophores in the skin (e.g., NADPH, porphyrin, urocanic acid), by irradiation of dermal collagen and elastin [79], or by irradiation of soluble proteins modified by advanced glycation end products [43]. The rise of ROS is observed within 1 min after UV A irradiation in mouse skin cells [85].

The extensive study of acute UV irradiation of the skin has greatly improved our understanding of the ROS-mediated activation of signaling cascades (Fig. 12.3.1).

Increased ROS levels following UV irradiation results in ligand-independent activation of several receptor-tyrosine kinases (RTKs) due to the inactivation of negative control exerted by the protein tyrosine phosphatases (PTPs). In the absence of ligand, RTKs are maintained in an inactive state by dephosphorylation by PTPs. ROS that are generated after UV irradiation oxidize a critical cysteine residue (present in all PTP catalytic sites) into sulfenic acid, thereby inhibiting the PTPs’ activity [9]. As a result, phosphotyrosines accumulate in the RTKs, mimicking the activation of the receptors that occurs upon ligand binding. UV irradiation can activate multiple RTKs simultaneously, thereby inducing a substantial cellular response [63]. In skin, epidermal growth factor receptor (EGFR) is the most abundant RTK in epidermal keratinocytes. EGFR has recently been shown to be a key mediator of UV-induced oxidative stress in cultured skin cells [83]. EGFR phosphorylation is controlled by receptor PTP kappa (RPTPκ) [81], which is inactivated following UV irradiation [82]. Inactivation of RPTPκ results in increased EGFR phosphorylation, even in the absence of ligand [82]. Increased EGFR phosphorylation occurs within 10 min after UV irradiation in human skin in vivo [16].

Cellular response that follows acute UV irradiation of human skin closely resembles that which follows ligand-mediated activation of cytokines and growth factor

![Fig. 12.3.1](https://example.com/fig1231.png) Mechnisms of photoaging- and natural aging-mediated alterations of skin connective tissue. **Acute response:** Aging and UV irradiation negatively regulate TGF-\(\beta\) signaling pathway, and generate reactive oxygen species (ROS), which together result in reduced new procollagen production and MMP-mediated fragmentation of existing collagen in the dermis. **Self-sustained response:** Collagen fragmentation that accumulates overtime or after repeated UV exposures reduces mechanical tension within the dermal extracellular matrix, which in turn inhibits procollagen production and raises MMP expression by resident fibroblasts. The result is a self-sustained collagen depletion, which leads to alterations of the structure and function of skin connective tissue in naturally aged and photoaged skin.
receptors (reviewed in [60]). These responses include recruitment of adaptor proteins, activation of the three families of mitogen-activated protein kinases (MAPks) (i.e., extracellular signal-regulated kinase [ERK], c-Jun amino-terminal kinase [JNK], and p38), transcription and functional activation of transcription factor c-Jun, which partners which constitutively expressed c-Fos to form the activated activator protein-1 (AP-1) transcription factor complex. UV irradiation-induced activation of MAPKs occurs throughout the epidermis and upper dermis [18]. c-Jun activation is detected 30 min to 1 h after UV exposure in human skin in vivo, and lasts for at least 24 h [17]. In sun-protected areas of the skin, age-dependant oxidative stress leads to similar activation (although to a quantitatively lesser extent) of signaling pathways, including activation of JNK and increased expression of AP-1 [7].

AP-1 is a critical regulator of several collagen-degrading enzymes, including matrix metalloproteinase (MMP)-1 (interstitial collagenase), MMP-3 (stromelysin 1), and MMP-9 (gelatinase B). Activated AP-1 increases production of these MMPs, which are responsible for the degradation of collagen fibers that maintain the structural network of the dermis. In parallel, AP-1 activation reduces synthesis of soluble collagen precursor (procollagen) by negatively regulating transcription of the genes encoding procollagen I and III.

The transforming growth factor-beta (TGF-β) signaling pathway, which is the major regulator of collagen formation in skin, is also altered during the aging process. In the dermis, TGF-β and its downstream mediator connective tissue growth factor (CTGF or CCN2) stimulate procollagen synthesis and down-regulate expression of MMPs, including MMP-1 [11, 59]. Interestingly, TGF-β type II receptor, which mediates TGF-β effects, and CTGF are down-regulated after UV irradiation in skin [56–58], and in aged and photo-aged human skin [59], thereby contributing to reduction of procollagen synthesis and elevation of collagen-degrading enzymes. In addition, cysteine-rich 61 (Cyr61 or CCN1), which functions to up-regulate MMP-1 and down-regulate procollagen production, is elevated in aged and UV-irradiated skin [59]. Whether Cyr61 is directly or indirectly regulated by oxidative stress and Cyr61 mechanism of action remain to be determined.

Altogether, ROS increase MMPs that degrade existing collagen and inhibits new collagen synthesis.

### 12.3.1.1.2 Extracellular Matrix Alterations Maintain the Aged Phenotype of the Skin

Aged or photoaged skin is characterized by a sustained imbalance between degradation and synthesis of dermal collagen. For instance, procollagen I production is reduced by 70% in aged vs. young human skin [75], and procollagen decrease correlates with the severity of photoaging [69]. How does increased ROS, which may be transient following UV irradiation or gradually increasing during aging, result in sustained extracellular matrix alteration in photoaged or aged skin? Recent studies partially answer this question.

Dermal fibroblasts isolated from photoaged and sun-protected skin of the same individual have similar growth and procollagen production capacities in culture, suggesting that impaired procollagen production of photoaged skin is not due to inherent genetic or epigenetic alterations following UV irradiation [73]. Similarly, dermal fibroblasts isolated from aged skin show only a moderate decrease in procollagen synthesis capacities in culture, which can only partially explain the substantial reduction of procollagen production observed in vivo [75]. These observations suggest that decreased procollagen production in aged and photo-aged skin is caused largely by alterations of an environmental factor rather than alterations of the fibroblasts themselves.

Transient increase in ROS results in MMP-mediated fragmentation of existing collagen in the skin. Fragmented collagen accumulates in aged and photo-aged skin [73, 75]. Reduced mechanical tension within the dermal extracellular matrix, which is brought about by collagen fragmentation, is thought to be responsible for the sustained reduction of procollagen production that is observed in aged and photoaged skin. In young, sun-protected skin, fibroblasts exert contractile forces on the surrounding collagen fibers, and conversely, the collagenous matrix exerts extracellular mechanical resistance that counterbalances cellular contractile forces. Fibroblast metabolic activities are controlled by mechanical tension [12, 35]. High cell-matrix tension promotes high procollagen and low MMP production, and vice versa [27, 35, 45, 46]. Similarly, the lack of mechanical tension that characterizes aged and photoaged skin results in low procollagen and high MMP production. This direct effect of mechanical tension on collagen homeostasis can be modeled in vitro using...
collagen gels partially digested with purified human MMP-1 [73]. Such treatment generates collagen fragments that morphologically resemble the ones observed in photoaged and aged skin in vivo. Interestingly, when normal fibroblasts are cultured on an MMP-1-degraded collagen substrate, their procollagen producing capacities are dramatically reduced when compared to cells cultured on an intact collagen gel [73].

Reduction of mechanical tension appears to be responsible for reduced procollagen synthesis and increased MMP production in aged and photoaged human skin. MMPs are responsible for degradation of existing collagen. Collagen fragmentation reduces mechanical tension, which in turn inhibits procollagen production and raises MMP expression. The resulting situation is thus self-sustained collagen depletion, which leads to the observed alterations of the structure and function of skin connective tissue.

12.1.2.2 Functional Changes Related to Skin Aging

Alterations of the structure of the skin that accompany the aging process have substantial impact on metabolic activities of the cells that reside within the dermis. Similarly, epidermal abnormalities also contribute to the altered function of aged skin. Aging affects many skin functions including mechanical integrity, sensory perception, immunologic responsiveness, thermoregulation, and wound healing.

With aging, the dermal–epidermal junction flattens, the number of interdigitations (rete pegs) dramatically decreases, resulting in a smaller contact surface area between the dermis and the epidermis. As a result, dermal–epidermal separation occurs more readily in elderly skin, and elderly skin is thus more likely to tear or blister. Reduced surface contact also compromises transfer of signaling molecules and nutrients between epidermis and dermis, affecting the mechanical, immunologic, and barrier functions of the epidermis.

Epidermal turnover rates decrease by 30–50% between 20 and 70 years of age. This decrease, along with decreased lipid synthetic capacity of keratinocytes, slows the replacement rate of the stratum corneum, likely resulting in a rougher skin surface and a less adequate barrier [23]. Slow replacement of the surface layer is also thought to contribute to the prolonged healing times for epidermal wounds in the elderly.

Decreased collagen content that accompanies the aging process results in thinning of the dermis, and alteration of fibroblast metabolism within the tissue, as described earlier. Collagen is not the only extracellular matrix protein that is affected by the aging process. Elastic fibers also decrease in number and diameter with aging [3, 71]. This phenomenon is responsible for decreased elasticity of aged skin. Similarly, altered production of proteoglycans, which normally bind water in the dermis and epidermis, contribute to loss of skin hydration [42]. Changes in vessel wall architecture, perhaps secondary to reduced structural integrity of the supporting extracellular matrix in the dermis, contribute to vascular fragility that increases susceptibility to skin bruising, a common clinical occurrence in the elderly.

Altogether, associated with decreased keratinocyte and fibroblast proliferative capacity [22], these alterations contribute to the decline of the major function of skin, i.e., to serve as a protective barrier that is able to restore itself during wound healing.

12.3.2 Clinical Characteristics

Although they share common molecular features, sun-protected aged and photoaged skins appear clinically different. The clinical hallmarks of aged skin are fine wrinkles, sagging, thinning, loss of underlying fat (leading to hollowed cheeks and eye sockets, and loss of firmness on the hands and neck), dry skin, and inability to sweat sufficiently to cool the skin.

Photoaging can result in more dramatic alterations of the appearance of the skin than natural aging. The extent of photodamage greatly depends on the degree of skin pigmentation and sun exposure. Darkly pigmented skin is more resistant to photoaging than fair skin, mainly due to higher concentration of melanin, which absorbs UV irradiation and thereby acts as a natural sunscreen [32]. Photoaged skin is characterized by the presence of deep wrinkles (furrows) and a “ropy” appearance of the skin, sallowness, mottled hyper-pigmentation, actinic lentigines (or “aged” spots), and telangiectasia. Telangiectasia result from passive vascular dilatation and increased vessel tortuosity, and are responsible for the reddish, “broken vessel” appearance of photoaged skin.
Because people are mostly bothered by visible signs of aging that affect the most commonly exposed parts of their skin, most antiaging therapies have been designed and tested for their ability to reverse the clinical signs of photoaging. However, many of these treatments would be expected to be equally efficacious for the treatment of clinical signs of natural aging.

### 12.3.3 General Therapeutic Outline

A myriad of treatments including many over-the-counter products promise to rejuvenate aged skin. However, very few treatments have been objectively tested for their ability to treat the clinical signs of photoaging.

Based on current knowledge regarding the molecular basis of photoaging, as described above, effective antiaging strategy implies breaking the downward spiral of the self-sustained loss and fragmentation of skin connective tissue. Thus, any drug or treatment that is able to stimulate new collagen formation, stop existing collagen degradation, remove collagen fragments, and/or restore mechanical tension in the skin should be considered a potential candidate for antiaging therapy. A few therapies have been proven to do so in clinical trials, and can be recommended by dermatologists as suitable treatment options to their patients seeking skin rejuvenation.

Antiaging therapy can be classified into three groups according to their mechanisms of action. The first group includes topically applied drugs that stimulate cellular metabolism in the skin and increase collagen deposition. Retinoids (vitamin A derivatives) and vitamin C belong to this group.

The second group includes injectable materials. This group includes wrinkle-smoothing drugs like Botox and dermal fillers. Dermal fillers are injectable materials used for soft-tissue augmentation. They are temporary (or resorbable, like collagen or hyaluronic acid), or permanent (nonresorbable, like silicone or microspheres). Most permanent fillers are not approved for wrinkle reduction in the USA but are used in Europe. Among them, injectable silicone was banned by the Food and Drug Administration in the early 1990s for its tendency to harden and cause skin necrosis. Fillers are used for volume augmentation to physically support the matrix underneath a wrinkle. They also locally increase the mechanical tension in the dermis and thereby stimulate procollagen production by fibroblasts (76) and see below).

The third class of antiaging therapies comprises resurfacing procedures. Laser treatments were first developed to selectively remove benign, pigmented, or vascular lesions that develop on the surface of the skin. Resurfacing procedures are now used to treat photoaged skin through epidermal and high dermal wounding, administered in a controlled manner. The resulting wound healing response promotes growth of new skin with improved structure, function, and appearance. Among these procedures, three methods are used to create controlled injury: chemical resurfacing (or peeling), mechanical resurfacing (dermabrasion), and laser resurfacing.

### 12.3.4 Current Established Therapies

#### 12.3.4.1 Topical Treatments

##### 12.3.4.1.1 Retinoids

Retinoids are a group of compounds characterized by vitamin A-like biological properties. They are the only family of drugs that have been extensively studied and proven efficacious for the treatment of clinical signs of aging. Tretinoin (all-trans retinoic acid) is approved in the United States and Europe for the treatment of photoaging. Other natural or synthetic retinoids (retinaldehyde, retinol, tazarotene) are also used for the topical treatment of photoaging.

The ability of retinoids to treat photoaged skin was first demonstrated in 1988 [77]. This vehicle-controlled study showed that 0.1% tretinoin cream applied to the face and forearms stimulates keratinocyte growth in the epidermis, improves dysplasia and atypia, promotes a more uniform dispersion of melanin, and increases neoformation of collagen and blood vessels. Since then, multiple vehicle-controlled double-blind studies confirmed these initial findings and tested different concentrations and regimens (reviewed in [24, 61]). Altogether, these studies showed that retinoids achieve clinical improvement, when applied once a day for 3 months or more. Clinical improvement of wrinkles and skin roughness persist with long-term use of tretinoin (9 months, up to 2 years), even when dose or frequency of applications are reduced [14, 33].
At the biochemical level, retinoids increase collagen I and III formation [26, 80], reorganize packed collagen fibers [84], increase the density of anchoring fibrils within the epidermal–dermal junction [80], and decrease MMP production [15]. On the other hand, retinoids have no discernable effect on solar elastosis.

12.3.4.1.2 Vitamin C

Since ROS are critical mediators of the aging process (Fig. 12.3.1), antioxidants are considered to be potential candidates for antiaging therapy. Many candidates exist such as vitamin C, vitamin E, coenzyme Q10, idebenone, and various botanical extracts. However, very few have been tested in more than one clinical, double-blind vehicle-controlled study, except for vitamin C.

Vitamin C (L-ascorbic acid) is a water-soluble vitamin supplied by the diet in humans, and naturally present in the dermis and the epidermis of rodent skin [66]. Vitamin C is an electron donor that neutralizes free radicals in the aqueous compartment of cells. The reduction of vitamin C is a two-step process that gives rise to dehydroascorbic acid, which can be enzymatically recycled into L-ascorbic acid or broken down. Vitamin C also promotes procollagen synthesis either directly [39], or as a cofactor of procollagen-processing enzymes [51]. Finally, vitamin C is involved in the regeneration of vitamin E (α-tocopherol, a potent lipophilic antioxidant) at the cell membrane [47].

A few clinical studies have found topical vitamin C to be beneficial for the treatment of photoaging. In a 3-month randomized, double-blind, vehicle-controlled study, Traikovich et al. showed that 10% ascorbic acid improved the clinical appearance of photoaged skin, as measured by optical profilometry of skin replicas of the crow’s feet area [70]. Clinical assessment showed improvement of fine wrinkling, tactile roughness, coarse rhytids, skin tone, sallowness, and overall features. A decrease of photoaging score was also reported after 12-week treatment of photoaged face with 10% L-ascorbic acid and 7% tetrahexyldecyl ascorbate (lipid-soluble derivative) in anhydrous polysilicone gel base [19]. Decrease of the deep furrows was observed after 5% vitamin C topical treatment of photoaged neck and forearms for 6 months [29].

Biochemically, topical vitamin C increases collagen transcription [52] and procollagen I protein expression [19] in human skin in vivo. Electron microscopy analysis showed evidence of elastic tissue repair in vitamin C-treated skin vs. placebo after 6 months of treatment [29], but no increase in elastin mRNA [52]. The limiting factor for using ascorbic acid in cosmetic formulations is its lack of stability in aqueous solutions. Previous studies conducted on pigs have shown that topical L-ascorbic acid can be formulated in a manner that enhances stability and skin penetration [55]. Such formulations are yet to be clinically tested to determine whether they are effective in treating the clinical signs of skin aging.

12.3.4.2 Injectables

Injectables are typically used for removing wrinkles at specific sites, mainly nasolabial and glabellar (frown) lines. They are either wrinkle-smoothing agents like Botox, or dermal fillers.

12.3.4.2.1 Botox

Clostridium botulinum produces the most potent neurotoxins currently known, and is responsible for botulism. Among the five botulinum toxins (BTXs), the BTX-A (or Botox) was first used for the treatment of strabismus, based on its ability to block neuromuscular junction and thereby decrease muscle contraction [65]. Botox injections are now used to decrease facial lines that are caused by repetitive muscle function. Botox paralyzes subcutaneous muscle contraction to give a smooth appearance to the overlying skin. Botox is approved for correction of the glabellar lines, in the USA, and for “face lines”, in Europe. Vehicle-controlled studies showed that Botox is effective in reducing crow’s feet [40] and glabellar lines [5, 6]. Repeated injections, up to three treatments, at 4-month intervals are more effective than a single injection, with the benefits of the second injection lasting longer than the first [21, 40]. Whether this effect is due to muscle atrophy that occurs with repeated injections needs to be determined.

Dose-response studies showed that a single dose of 12 units is the most efficient in treating crow’s feet lines [41], and that patients injected with 10 units of Botox relapsed faster than patients injected with 20, 30, or 40 units [6].
12.3 Aging and Photoaging of the Skin

12.3.4.2.2 Dermal Fillers

Soft-tissue fillers are used to mechanically support dermal depressions underlying wrinkles due to loss of collagen or repetitive muscle function. They are primarily used for nasolabial and glabellar folds, and deep wrinkles. Ideally, skin fillers are biocompatible, non-immunogenic, non-migratory, pliable, painless, and keep their property overtime. In reality, there is no perfect filler.

The major side effect of fillers is the development of immunologic reactions, which can lead to granuloma formation. Side-reactions are generally mild with temporary fillers, and disappear with the filler, which has a limited lifetime. On the other hand, permanent fillers have longer lasting effects, but may also provoke reactions that persist for months or years after injection.

Before considering any skin filler treatment, practitioners should carefully evaluate the risk/benefit ratio of each option and discuss them with their patients. All fillers can lead to adverse events and patients need to be fully informed of the risk before the procedure [1]. Unfortunately, very few evaluator-blinded comparisons of safety and efficacy have been conducted to guide clinicians in their choice.

Temporary Fillers

Temporary fillers can be categorized in three groups. First, animal collagens (bovine, porcine), have been widely used since injectable skin fillers were first introduced in the 1970s. Long-term experience has found them to be generally safe. Because of their animal origin, they require skin testing for allergy before use (two skin tests are performed 2 weeks apart, with the second being 4 weeks before the procedure). About 3% of patients develop local adverse effects that include erythema, induration, pruritus, and skin discoloration. Clinical effectiveness lasts 3–6 months, with a regression of filling effect linear with time [64].

Second, collagens of human origin have recently been developed to eliminate the requirement for skin testing. Thus, patients may undergo treatment at the time of their initial visit. Human collagens are extracted from human tissue or cell culture. Their preparation is expensive, but their use is considered safer than animal collagen because they are not allergic [4]. Bruising and edema have been reported with the use of human collagen fillers. Their clinical effects last 3–6 months, and disappear when the filler is degraded in situ [44]. The third group of temporary fillers comprises hyaluronic acid (HA)-based fillers. HA is a glycosaminoglycan (a polymer consisting of D-glucuronic acid and D-N-acetylglucosamine). HA is a natural component of the skin extracellular matrix in the dermis and epidermis, and has natural water-holding properties. HA has a half-life of 12 h to a few days [2]. Thus, HA must be stabilized by cross-linking to increase its stability as skin filler. Clinical improvement typically lasts 3–12 months, depending on the type of filler used and the individual.

Permanent Fillers

Permanent (or semi-permanent) fillers are in use in Europe for correcting wrinkles, whereas only one (Radiesse®) is approved in the United States for this purpose. The most common types of permanent fillers are made of polyacrylamide gels, acrylate-containing microspheres, or silicone. Permanent fillers are useful for their long-lasting effects but present several disadvantages. First, their effects are highly dependent on the technique of injection. Second, they tend to move over time due to muscle movement and create lumps on the edge of wrinkles. Finally, they can cause granulomatous reactions. For these reasons, the use of permanent fillers should be limited.

Mechanisms of action

Despite the dramatic rise in the use of dermal fillers, very few studies have addressed the mechanisms of action of these compounds. Immediately after the injection, the smoother appearance of the skin is thought to result from restoration of lost volume due to collagen degradation that occurs during aging. However, it is not clear whether the implant elicits cellular or molecular responses within the skin. The presence of cross-links was shown to increase the lifetime of bovine collagen filler, allowing massing of fibroblasts around the periphery of the implant [37]. Fibroblasts subsequently invaded the implant and provoked an inflammatory reaction followed by replacement of the implant by new endogenous collagen [37]. A different mechanism has recently been described after injection of a cross-linked HA filler, for which no
inflammatory reaction was observed. Instead, injection of the cross-linked HA filler was shown to locally increase mechanical tension in the dermal extracellular matrix, thereby stimulating procollagen production by fibroblasts in the vicinity of the implant [76]. Thus, increased procollagen production likely contributes to the clinical benefits derived from dermal filler injections. Interestingly, this last study demonstrates that mechanical stretch can be used to restore collagen producing capacity of fibroblasts in photoaged skin in vivo. More studies will be needed to determine whether skin responds similarly to all dermal fillers, and/or to different forms of mechanical stretch.

12.3.4.3 Resurfacing Procedures

Resurfacing techniques involve the use of chemical, mechanical, or laser devices to create a wound in a controlled manner. The resulting wound healing response stimulates regeneration of skin with improved appearance and function. The amplitude of the response (regeneration) is proportional to the wound depth, which should be chosen according to the extent of skin damage. These procedures should not be performed on patients with abnormal healing or on medication that interferes with the healing response.

Chemical peels involve the application of chemicals to the skin that stimulate regeneration of new skin cells. Chemical peels are broadly classified as superficial, medium, and deep peels, according to the depth of injury they create. Very few clinical studies have been performed on most types of chemical peels, except for the superficial peeling agents alpha-hydroxy acids, which have been shown to induce a moderate increase in skin thickness after 4–6-month treatment [10, 67]. More vehicle-controlled studies are needed to evaluate the benefit of various peeling agents.

Dermabrasion consists of removing the surface of the skin with an abrasive tool such as a wire brush or a diamond fraise. Abrasion is obtained by jets of zinc or aluminum oxide crystals, fine organic particles, or a roughened surface. Particles and skin debris are vacuumed off through the hand piece through which the abrasive particles are delivered. Dermabrasion techniques also include the milder microdermabrasion, which abrades the stratum corneum (outermost cornified layer of the epidermis).

CO₂ laser resurfacing is an ablative technique that uses high-energy irradiation to remove the epidermis and superficial dermis. The CO₂ laser delivers short bursts of extremely high-energy irradiation that vaporizes the epidermis by heating. In contrast, the erbium:yttrium-aluminum-garnet (Er:YAG) laser produces energy that penetrates into the skin. The energy is readily absorbed by water in tissue cells, limiting the heat effects within the tissue. Deep resurfacing procedures require local or regional anesthesia. More detailed descriptions of lasers used in dermatology are provided in Chap. 1.10.

Several studies have demonstrated the clinical and biological effects of dermabrasion and CO₂ laser resurfacing procedures for the treatment of the clinical signs of aging. Both procedures induce a wound healing response that promotes repair of the damaged skin [34, 53]. An inflammatory reaction (monitored by the levels of interleukin-β and tumor necrosis-α inflammatory cytokines) develops within the first week after a single CO₂ laser treatment. The inflammatory reaction is accompanied by an increase in extracellular matrix-degrading enzymes (MMP-1, -3, -9, and -13). MMPs peak within the first 10 days after treatment, and remain elevated for at least 30 days. This phase of matrix turnover is followed by deposition of new collagen, beginning at approximately 21 days after treatment, and continuing for at least 6 months [53].

Dermabrasion and CO₂ laser increase dermal TGF-β1 levels and procollagen I formation, which correlates with clinical improvement [34, 49, 50, 54]. Interestingly, the amplitude of the response is proportional to the degree of injury: CO₂ laser treatment that removes the interfollicular epidermis and the superficial dermis strongly stimulates procollagen production [53], whereas injury and response are less pronounced with dermabrasion [34, 49]. Conversely, no dermal remodeling is achieved if the abrasive component of microdermabrasion is omitted [34]. Overall, greater clinical improvement can be achieved with CO₂ laser when compared with dermabrasion [36].

12.3.5 Experimental Approaches

The lack of good animal models that faithfully recapitulate alterations that occur in aged and photoaged human skin hampers the development of new or improved skin aging therapies, and the elucidation of detailed molecular
basis of existing treatments. Structure and function of rodent skin differ significantly from human skin. Pig skin more closely resembles human skin. However, pigs live a relatively long life (~15 years), and husbandry is complicated and expensive.

Cell culture systems also have significant limitations. For instance, human dermal fibroblasts in culture constitutively produce high levels of procollagen that can hardly be further increased by collagen-stimulating treatments (L Rittié, GJ Fisher, unpublished observations). Moreover, skin organ cultures have limited lifetime, and xenograft of human skin on the back of immunodeficient mice require an elaborate laboratory setting.

Recently, a three-dimensional collagen gel fibroblast culture model that resembles the environment of aged and photoaged skin has been described [73]. Treatment of collagen gels with human MMP-1 generates collagen fragments that are similar to those observed in aged and photoaged human skin in vivo [20, 75]. When dermal fibroblasts are seeded in a MMP-1-treated collagen gel, procollagen production is significantly reduced, compared to fibroblasts cultured in intact collagen gels [74]. This model may be helpful for better understanding mechanisms that regulate collagen homeostasis in aged and photoaged human skin.

### 12.3.6 Complications to Avoid

#### 12.3.6.1 Complications to Skin Aging

In addition to causing undesirable appearance of the skin, photoaging is associated with DNA damage that can lead to the development of precancerous and cancerous lesions. Squamous and basal cell carcinomas (SCC and BCC) are clearly linked to UV irradiation exposure, with the great majority occurring on sun-exposed areas of fair-skinned individuals [38, 72]. Clonal mutations of p53 in keratinocytes are a hallmark of photoaged skin [30]. They are also found in actinic keratosis and more than 90% of SCCs [86]. The presence of p53 mutations is considered a marker of elevated risk of cutaneous carcinoma [8]. Interestingly, some cosmetic treatments such as dermabrasion and CO₂ laser remove the p53-mutated keratinocytes in the epidermis [13, 53]. Follow-up studies are needed to determine whether this treatment decreases the incidence of cancerous lesions in patients at high risk for the development of skin cancer.

Delayed wound healing is common in aged individuals, and is characterized by decreased levels of growth factors, diminished cell proliferation and migration, and reduced extracellular matrix production [25]. To date, there is no evidence that any of the treatments described above are beneficial for improving wound healing in elderly individuals.

#### 12.3.6.2 Complications to Therapy

Each therapeutic option described above has advantages and disadvantages. Topical therapies are considered the safest, but clinical improvement requires several months. No major side effect has been reported with topical vitamin C therapy. The major side effect of retinoid therapy is “retinoid dermatitis” or irritation and scaling of the skin. Up to 92% of subjects who used retinoic acid have reported such side effects [77]. Retinoic acid-induced skin hyperplasia is due to increased keratinocyte growth, which results from stimulation of epidermal growth factor receptor (EGFR)-mediated mitotic response in the epidermis [62]. Retinoid dermatitis can be lessened by decreasing dose or frequency of treatment, use of retinoic acid precursors such as retinol or retinaldehyde, of which only a small fraction is converted to retinoic acid by skin cells, or by simultaneous treatment with natural EGFR inhibitors such as genistein [62].

The most common adverse effects of Botox injections are pain, bruising, and headaches. Eyelid and brow ptosis (drooping) may occur with inappropriate injection technique [78]. Injection techniques are also critical with dermal fillers, which can create lumps if not administered properly. Such “errors” have less consequence with temporary fillers, which eventually are resorbed. However, permanent fillers can leave permanent nodules. Whether these past “complications” were the results of large volume injections or adulterated materials is still subject of controversy [48].

Postoperative erythema occurs in all patients treated with laser resurfacing, and is considered a transient side effect. Although laser resurfacing is considered safe if administered by competent medical personal, persistent erythema, hypo- or hyperpigmentation, scarring, and wound infection have been reported in a non-negligible
portion of treated patients [68]. These complications should be expected by both the surgeon and the patient, monitored closely after the procedures, and managed accordingly.

Take Home Messages

- Natural aging and photoaging are clinically distinct, but share major biochemical and cellular similarities including loss of mechanical tension in the dermis. Decreased mechanical tension is a key driving force that leads to sustained loss of dermal collagen, the major structural component of the extracellular matrix that supports the skin. Loss of mechanical tension is the result of chronic degradation of the collagen network that supports fibroblasts in the dermis, and is caused by overproduction of collagen-degrading enzymes. These enzymes are produced in response to increased ROS levels in the skin, which occur with natural aging and after UV irradiation. Repeated sun exposures lead to photoaging, which can be considered, to some extent, as an accelerated form of natural aging. Restoring skin properties in aged skin involves restoring the balance between production and degradation of collagen, which includes restoring mechanical tension in the dermis. Clinical improvement of aged skin, which is typically preceeded by increased procollagen production in the dermis, can be achieved by several established therapies. Options for the development of new antiaging therapies include reducing ROS levels, restoring proper mechanical tension in the skin, and/or increasing collagen deposition in the dermis.

References

12.4 Occupational Dermatoses

S. Mark Wilkinson and Pieter-Jan Coenraads

12.4.1 Introduction

This chapter includes many disorders that are covered elsewhere and aims to highlight aspects that are specific to an occupational causation and prevention.

A household survey of occupational illness in the UK estimated a rate of 15 per 10,000 of those who had been employed. In Scandinavian countries, where reporting of occupationally related disease by physicians is mandatory, there is a reported incidence of 5.1 per 10,000. The relative frequency of occupational dermatoses seen by dermatologists and occupational physicians differs and reflects the varying industries served by both and the latency in the development of skin cancer (Table 12.4.1) [1]. All but 4% of cases of skin cancer were attributed to UV irradiation. In the USA, over time the relative importance of occupational skin disease has fallen to 10–15% of all occupational illness partially due to a rise in musculoskeletal disorders [2]. It was estimated that in 1984 the annual cost to the US was between $222 million and $1 billion. In the early 1990s estimated costs for lost time were $1,881 per claim with 9% of claims involving more than 3 days off work. The relative incidence by industry is shown in Table 12.4.2.

12.4.2 Contact Dermatitis

The treatment of dermatitis is discussed in Chap. 4.1.

12.4.2.1 Chemical Burns

12.4.2.1.1 Etiology and Pathophysiology

Burns occurring during work are relatively common with an annual incidence of 26.4 per 10,000 workers accounting for 29% of burns admitted to hospital. Injury usually occurs to the hand, wrist, or eye. Most are caused by heat or chemical exposure. Damage is so severe that cell death results.

Key Features

- Skin disease caused or aggravated by an individual’s employment
- Typically affecting the hands
- Most often contact dermatitis

Key Features

- Acute irritant reaction in which injury is irreversible [3, 4]
- Initial burning and erythema
- Leads to blisters, erosions, and ulceration
- Chemical absorption causes systemic symptoms

12.4.2.1.1 Etiology and Pathophysiology

Burns occurring during work are relatively common with an annual incidence of 26.4 per 10,000 workers accounting for 29% of burns admitted to hospital. Injury usually occurs to the hand, wrist, or eye. Most are caused by heat or chemical exposure. Damage is so severe that cell death results.
Typically acids coagulate proteins forming a barrier limiting the extent of the injury while alkalis result in a liquefactive necrosis that aids penetration. In dermatological practice, cement burns [5] may be encountered (Fig. 12.4.1) although they account for only 1.8% of adult burns. Calcium oxide (lime) reacts with water to form calcium hydroxide with a pH of 12–13 within 2 min. The high alkalinity persists for 8–14 h until formation of calcium carbonate by carbon dioxide in the air. Third-degree burns may develop with 1 h of exposure although the burn may take several more hours to develop.

Table 12.4.1 Relative frequency of occupational dermatoses seen by occupational physicians and dermatologists

<table>
<thead>
<tr>
<th></th>
<th>Dermatologist (%)</th>
<th>Occupational physician (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact dermatitis</td>
<td>79</td>
<td>80.2</td>
</tr>
<tr>
<td>Contact urticaria</td>
<td>3.5</td>
<td>4.7</td>
</tr>
<tr>
<td>Folliculitis/acne</td>
<td>0.5</td>
<td>0.9</td>
</tr>
<tr>
<td>Infective</td>
<td>2.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Mechanical/traumatic</td>
<td>1.6</td>
<td>1.2</td>
</tr>
<tr>
<td>Nail disease</td>
<td>0.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>12.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Other</td>
<td>9.9</td>
<td>7.7</td>
</tr>
</tbody>
</table>

Superficial partial thickness burns involve the epidermis to the level of the dermal papillae and appear erythematous and wet. The skin blanches and is painful as the vasculature and nerves are preserved. Healing usually occurs without scarring over 2 weeks.

Deep partial thickness burns extend into the dermis but appendages are spared. The skin appears pale and oedematous with blisters present. Pressure may still be felt. Healing begins from the adnexal remnants and takes up to 6 weeks to occur with scarring.

Full thickness burns extend into the subcutaneous fat appearing white to brown/black eschar that is dry to the touch. The skin is anaesthetic and healing is slow to occur from the periphery of the injury with significant scarring and risk of contracture.

12.4.2.1.3 General Therapeutic Outline

The extent of injury is determined by the nature of the chemical and the duration of contact. Accordingly, initial treatment is based on limiting chemical exposure to minimize the extent of the burn. It is essential to remove contaminated clothing and remove any residual chemical at the work place by washing in water ideally under a low-pressure shower. Immersion in a bath potentially dilutes the chemical without removing it from the skin. For acid burns up to 2 h and for alkali burns up to 12 h may be required. Blisters and necrotic skin should be debrided as they may contain residual chemical. Extensive burns require skin grafting to cover the defect.
12.4.2.1.4 Current Established Therapies

Some chemicals require specific treatment. Oxidizing agents such as bleach (sodium hypochlorite) and chromic acid coagulate protein. The application of milk or egg whites can form an alternate substrate for the chemical thus reducing damage to the skin before irrigation. Similarly reducing agents such as hydrochloric, nitric, and sulfuric [6] acids can be neutralized with soap, sodium bicarbonate, soda lime (a mixture of sodium and calcium hydroxides), or magnesium hydroxide before lavage. Irrigation however should not be delayed if an antidote is not immediately available as the time to treatment is a major predictor of extent of subsequent tissue damage. Phosphorus is used to make fireworks and is also found in a military context. Particles need to be removed manually and can be made visible with a brief wash in copper sulfate 1% to stain the particles black before irrigation [7]. Systemic absorption of phosphorus may affect calcium metabolism (vide infra).

For some chemicals water lavage is not appropriate.

- Phenols used in industry for the manufacture of plastics and cleaning agents are not water soluble and need to be wiped immediately from the skin with undiluted polyethylene glycol. If there is delay phenol penetrates the skin rapidly resulting in neuropathy. Vasoconstriction can also contribute to the necrosis and systemic absorption result in renal damage and shock.

- Chemicals such as pure sodium, potassium, and lithium react with water igniting spontaneously. Initially the fire must be extinguished. Class D fire extinguishers are designed for use with burning metal but each is designed for a particular material and should not be used indiscriminately. Finely ground sodium chloride and graphite can be used on most but powdered copper is preferred for lithium. In the absence of an appropriate extinguisher, dry sand can be used. Once extinguished the burn should be covered with mineral or cooking oil to isolate the metal from water and allow the fragments to be removed.

With some chemicals, there may be significant systemic absorption.

- Chromic acid [8] used for electroplating and in the dye industry can cause systemic involvement following a burn affecting as little as 1% of the body surface area. Acute systemic absorption is associated with hepato-renal failure, gastrointestinal hemorrhage, central nervous disorders, anaemia, and coagulopathy. Absorption can be prevented by converting the hexavalent chromium to its trivalent state with phosphate buffer, 5% thiosulfate, or 10% calcium ethylene diamine tetra-acetic acid. Immediate excision has been recommended as an effective means of reducing the risk along with peritoneal or hemodialysis to remove any absorbed chromium. Peak blood levels are reached about 5 h after exposure when levels begin to fall as hexavalent chromium taken up by red blood cells is reduced to the trivalent state bound to hemoglobin. At this point, the chromate can only be removed by exchange transfusion. Uptake by other tissues results in trivalent chromate bound to intracellular protein in various affected organs.

- Hydrofluoric acid [9, 10] is used in glass, ceramic, semiconductor, chemical, and oil refining industries the treatment of textiles and manufacture of pesticides. Burns may look innocuous on initial inspection but a 2.5% burn has a 10% mortality after exposure to 70% hydrofluoric acid. Hydrofluoric acid readily diffuses through lipid membranes and dissociates to release fluoride ions. Fluoride reacts with calcium and magnesium to form insoluble salts that then cause tissue destruction and severe pain in the subcutaneous tissues. Electrolyte imbalance due to lack of availability of calcium and magnesium may result in arrhythmia and death. Symptom onset is usually immediate with anhydrous hydrofluoric acid but can be delayed up to 24 h with dilutions below 20%. Immediate treatment involves irrigation for 20 min and removal of contaminated clothing. If the burn meets any of the criteria in Table 12.4.3, the individual should be sent to an emergency unit for treatment of the potential electrolyte imbalance. Topical 2.5% calcium gel should be applied with the aim of relieving pain which is a marker for the presence of free fluoride. For this reason, local anaesthesia should not be used. The gel should be rubbed in for at least 30 min repeated if pain returns. Other topical treatments that precipi-
Hydrofluoric acid burns likely to induce electrolyte imbalance

<table>
<thead>
<tr>
<th>Area involved</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>100%</td>
</tr>
<tr>
<td>5%</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>7%</td>
<td>50–70%</td>
</tr>
<tr>
<td>10%</td>
<td>20–50%</td>
</tr>
<tr>
<td>20%</td>
<td>&lt;20%</td>
</tr>
<tr>
<td>Inhalation/ingestion</td>
<td>&gt;5%</td>
</tr>
<tr>
<td>Delay in treatment</td>
<td></td>
</tr>
<tr>
<td>Prolonged exposure</td>
<td></td>
</tr>
</tbody>
</table>

The severity of injury reflects the subsequent damage with large burns causing significant scarring (within which malignancy may develop), contractures, and nerve entrapment. Chemicals that penetrate easily through tissue may cause neuropathy and with systemic absorption hepato-renal damage and cardiac toxicity.

A burn resulting from a chemical sensitizer may result in skin sensitization and patch testing following the event may be valuable with a widely distributed chemical such as methylchloro and methylisothiazoline. Posttraumatic eczema, usually in a discoid pattern, can also follow skin injury including burns.

### 12.4.2.1.6 Global Variations

Variation in treatment largely reflects availability of specific therapies.

### 12.4.2.2 Irritant Contact Dermatitis

- Chemical exposure induces a cellular response but not cell death [11]
- Severity of injury related to speed of onset
- Itch
- With erythema, vesiculation, and hyperkeratosis
12.4.2.2.1 Etiology and Pathophysiology

In a survey of occupational skin disease reporting by both dermatologists and occupational physicians, the annual incidence of contact dermatitis was 12.9 per 100,000 workers. The incidence in men increased from 4.9 per 100,000 at age 16–29 to 6.6 at 45–60 years [1]. Conversely in women a higher rate 9.5 was seen in the younger age group falling with age. This reflects variation in type of employment with high rates in young workers associated with wet work and in older workers with exposure to oils irrespective of gender. Common causes of occupational irritant and allergic dermatitis [12] are summarized in Table 12.4.4.

Irritant dermatitis results when the skin’s defences and repair mechanisms are overcome. For some strong irritants, this may occur following the first exposure but more commonly a subclinical insult when repeated results in a cumulative irritant dermatitis the onset of which may be delayed for months or years after initial exposure.

12.4.2.2.2 Clinical Characteristics and Diagnosis

Irritant contact dermatitis is essentially indistinguishable from allergic contact dermatitis and endogenous eczema. The diagnosis is clinical reliant on a history of exposure and the time course of response. In the majority of individuals, the hands are affected and to a lesser extent the head and neck if the irritant is air borne. Some clinical features suggest an irritant dermatitis including preferential involvement of the web spaces on the hands and the presence of dry scaling on the dorsum (Fig. 12.4.2).

12.4.2.2.3 General Therapeutic Outline

Once developed, the mainstay of treatment is to minimize exposure to the precipitant. Ideally this would be through an alteration in the production process that prevents exposure but in practice personal protective equipment is often used. It needs to remembered that the type of gloves used should be appropriate for the exposure. While latex gloves are appropriate for most water-based exposures, they are unsuitable for solvents when nitrile gloves are often more suitable.

Symptoms can be palliated with the use of emollient and topical steroid. The effectiveness of topical steroids in treating irritant dermatitis has been questioned, [13] although this may reflect the nature of the
irritant and the presence or absence of an inflammatory response to the exposure.

### 12.4.2.2.4 Current Established Therapies

Treatment of eczema/dermatitis is discussed in detail in Chaps. 4.1 and 5.1.

#### Prevention

During pre-employment screening, a history of atopic eczema particularly with hand involvement indicates an individual at risk of developing irritant dermatitis and a dry job without significant wet work may be a better career option. Other risk factors for the development of irritant hand dermatitis include the presence of a contact allergy and another, as yet undefined, genetic risk factor [14].

Once in the work environment, a number of factors have been shown to influence the development of dermatitis and skin care packages have been developed for various professions such as hairdressers and nursing staff. An essential component of all of these, however, is the education of the workforce [15] resulting in a modification of behavior during work and reduction in skin symptoms. Factors that should be addressed are summarized in Table 12.4.5.

- Barrier creams are often used to prevent irritant contact dermatitis but in many situations it is thought that they act as no more than an emollient. Moisturizers [16] are of three main types. Occlusive substances block transepidermal water loss (TEWL) such as petrolatum and lanolin. Humectants such as glycerine and propylene glycol are hydroscopic and absorb water from the underlying tissues into the stratum corneum. These may increase TEWL if not combined with a film-forming substance. Hydrocolloids like colloidal oatmeal form an artificial membrane that physically impairs TEWL. Regular use of emollients on normal skin prior to irritant exposure has been shown to vary from increase, decrease, and have no effect on the damage due to subsequent irritant exposure. The effect varies with the composition of the moisturizer and the chemical irritant used. However, when exposure to a detergent hand wash was combined with use of emollient, this has been shown to reduce the development of irritant dermatitis. Further, once developed studies demonstrate that emollients consistently enhance repair and improve irritant dermatitis.

Barrier creams may therefore need to be specifically formulated for the intended exposure as is the case in allergic contact dermatitis where quaternium 18 bentonite and a topical protectant containing perfluoralkylpolyether have been shown to prevent reactions to

<table>
<thead>
<tr>
<th>Advice</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wash</strong> your hands in lukewarm water</td>
<td>The severity of irritation from detergent is temperature dependant</td>
</tr>
<tr>
<td><strong>Rinse and dry your hands thoroughly</strong></td>
<td>Wet work is a major risk factor for the development of irritant dermatitis</td>
</tr>
<tr>
<td><strong>Use protective gloves when undertaking wet-work</strong></td>
<td>Prolonged use of gloves leads to impairment of the skin barrier</td>
</tr>
<tr>
<td><strong>Wear gloves for as short a time as possible</strong></td>
<td>Shown to reduce the effect of glove occlusion on barrier function</td>
</tr>
<tr>
<td><strong>Wear cotton inner gloves when occlusive gloves are worn</strong></td>
<td>Occlusion of irritants by gloves enhances their irritancy</td>
</tr>
<tr>
<td><strong>Apply moisturizers</strong> during the day and after work</td>
<td>Promote the regeneration of epidermal barrier once damaged</td>
</tr>
<tr>
<td><strong>Use a lipid rich moisturizer</strong></td>
<td>More rapid healing</td>
</tr>
<tr>
<td><strong>Avoid fragranced products; some preservatives</strong></td>
<td>These are common causes of allergic contact dermatitis</td>
</tr>
<tr>
<td><strong>Apply to all of the hand</strong></td>
<td>As with hand washing some areas are typically omitted</td>
</tr>
<tr>
<td><strong>Follow the same advice at home</strong></td>
<td>Domestic/hobby exposures are additive</td>
</tr>
</tbody>
</table>
poison ivy and creams containing the chelator diethylentriamine penta-acetic acid reactions to nickel, cobalt, and copper [17].

- Gloves need to be carefully chosen for the specific chemical exposure. Chemicals permeate glove materials and the properties of a specific glove can be broken down into the breakthrough time and the rate of penetration. In general, the thicker the glove the longer the breakthrough time. Degradation occurs when a chemical reacts with the glove material impairing its physical properties. Permeation and degradation of a glove by a specific chemical are not necessarily related. Many of the major industrial glove suppliers have on their web sites tables detailing suitable gloves for specific chemical exposures and probable safe periods of use (e.g., www.ansell-edmont.com). Other conditions of use should always be borne in mind; for example, use of gloves in metal machining runs the risk of tears to the gloves and, if the glove is caught in the machinery, trauma to the hand. Some typical exposures and appropriate gloves are listed in Table 12.4.6

- Alcohol gel in the health care environment, as an alternative to a detergent based disinfectant, has been shown to be less irritating to the skin [18] as well as being a more effective means of disinfection.

12.4.2.2.5 Experimental Approaches

Anti-irritant is a term coined for chemicals that reduce the irritant potential of other more irritating ingredients in the same product. In a recent study, only glycerol was shown to modulate the irritant response induced by 1% sodium lauryl sulfate and 20% nonanoic acid in n-propanol in a dose-dependant fashion [19].

12.4.2.2.6 Complications to Avoid

Initially irritant dermatitis is reversible but as the disease persists the condition can become chronic such that even with complete avoidance dermatitis can persist a condition known as persistent post-irritant dermatitis. In some studies, this has affected up to 10% of the cohort involved [20].

Irritant dermatitis may also provide immunological stimuli that increase the risk of sensitization (both type I and IV) to contact allergens to which an individual is co-exposed [21].

Take Home Message

> Irritant dermatitis is potentially preventable. If exposure cannot be avoided by appropriate engineering of the production process education of the workforce in the risks and methods of prevention is essential.

12.4.2.2.7 Global Variations

Variations in the prevalence of irritant dermatitis and facilities available for prevention may reflect differences in expectations of the work environment and availability of mechanization to reduce exposure to the irritant.

12.4.2.3 Allergic Contact Dermatitis

See Chap. 5.1

<table>
<thead>
<tr>
<th>Table 12.4.6 Gloves suitable for some common chemical exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exposure duration</strong></td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>Detergents; cleansers</td>
</tr>
<tr>
<td>Solvents</td>
</tr>
<tr>
<td>Corrosive agents</td>
</tr>
<tr>
<td>Cutting fluids</td>
</tr>
</tbody>
</table>

NRL = natural rubber latex; PE = polyethylene; PVC = polyvinyl chloride; Ni-nitrile; Ne = neoprene; B = butyl rubber; VA = vinyl alcohol laminate
In an occupational setting it needs to be remembered that some allergens such as acrylates (nail technicians, dentistry, and orthopaedics), p-phenylene diamine, and glycerol monothioglycolate (hairdressing) penetrate rubber gloves and once sensitized may give false reassurance. As with irritants the choice of personal protective equipment needs to be chosen carefully for the specific exposure.

12.4.3 Contact Urticaria and Protein Contact Dermatitis

### Key Features
- Itch [22]
- Wheal and flare
- Within minutes of exposure
- Resolves within 24 h

### 12.4.3.1 Etiology and Pathophysiology

The causes of occupational contact urticaria [23] are summarized in Table 12.4.7. In general, contact urticaria may be caused through non-immunological means typically through the chemical action of low molecular weight chemicals or immunologically following the induction of IgE mediated hypersensitivity by protein or rarely low molecular weight chemicals. The prevalence of contact urticaria to low molecular weight chemicals is low and the vast majority of cases of occupational contact urticaria are immunologically mediated. Occupations at risk include predominantly agricultural workers, food handlers, and those required to wear latex gloves such as medical and dental staff.

Protein contact dermatitis [24] describes the situation in which an initial IgE-mediated reaction progresses to the development of an eczematous response and typically occurs to a similar range of protein antigens. The concept could be extended to include those instances in which a protein allergen such as latex [25] induces an eczematous response in the absence of contact urticaria.

### 12.4.3.2 Clinical Characteristics and Diagnosis

Symptoms may vary from the nonspecific with itch and other sensory symptoms to typical urticaria with a wheal and flare (Fig. 12.4.3). Onset is usually within 30 min of exposure at the site of contact with resolution over several hours. Immunologically mediated urticaria may progress to systemic symptoms with rhino-conjunctivitis, oro-laryngeal and gastrointestinal signs, asthma, and anaphylaxis.

Diagnosis relies on an accurate history for the disorder to be suspected. Confirmation may be by means of measurement of specific IgE if the antigen has been characterized and isolated to enable measurement of reacting antibodies in serum. For many allergens this may not be available or the blood test not sufficiently sensitive. In this instance, a commercial allergen extract with high sensitivity may be available and a skin prick test undertaken. Alternatively, it may be necessary to undertake a prick-prick test in which the raw allergen is initially loaded onto a lancet before pricking into the patient’s skin. Readings are taken at 15–20 min with positive histamine and negative diluent controls. A positive reaction is usually taken as a response 3 mm greater than the negative control, although doubtful reactions should always be interpreted in light of the history. Rarely if investigation is negative and contact urticaria still suspected it may be
12.4 Occupational Dermatoses

worth undertaking a use test in an attempt to reproduce normal exposure and see if urticaria can be induced.

When investigating protein contact dermatitis, the allergen may need to be tested on previously affected skin.

12.4.3.3 General Therapeutic Outline

Once sensitized, the allergy tends to persist and desensitization for most allergens is not available. The prime method of treatment is therefore of avoidance either by modification of the working environment or the use of personal protective equipment. Rarely, if avoidance is not possible a change of occupation may be necessary.

When exposure occurs urticaria can usually be controlled symptomatically with the use of antihistamines. If the patient is at risk of systemic involvement the prescription of hand-held adrenaline may be necessary.

For a number of allergens, there may be recognized cross-reaction patterns and if contact urticaria is diagnosed enquiry should be made to exclude allergy to other cross-reacting allergens; as is the case with latex and foods such as avocado, chestnut, banana, and kiwi [26].

12.4.3.4 Current Established Therapies

Treatment of urticaria is discussed in detail in Chap. 4.3

12.4.3.4.1 Prevention

Risk factors for the development of contact urticaria include those with high exposure to the allergen, the presence of hand dermatitis, and a genetic background of atopy. Of these, exposure and hand dermatitis are potentially amenable to modification. Reduction in exposure with the use of low protein, powder-free gloves has been shown to reduce the incidence of latex contact urticaria in a medical environment [27] (Fig. 12.4.4). While measures to reduce the presence of hand dermatitis might also be expected to be beneficial this has not been studied.

12.4.3.5 Experimental Approaches

Immunotherapy has been found to be effective for some allergic diseases where a specific allergen is the
cause of symptoms as is the case in grass pollen allergy. Various studies have looked at the application of a similar process to latex allergy, although as yet there is an unacceptable incidence of adverse effects [28].

12.4.3.6 Complications to Avoid

Anaphylaxis and death have been reported following exposure to type I allergens. More severe symptoms follow mucosal exposure when there may be greater absorption of allergen.

12.4.3.7 Global Variations

Variations in the prevalence of occupational contact urticaria reflect differences in industry and exposure of the work force around the globe.

12.4.4 Chemically Induced Acne

See Chap. 6.1

12.4.4.1 Chloracne

Key Features

- Comedones behind the ears
- Cysts and comedones with little inflammation on cheekbones and scrotum
- Systemic symptoms only in very severe cases
- Usually systemic exposure to causative chemicals

12.4.4.1.1 Etiology and Pathophysiology

Chloracne is caused by specific chlorinated (or brominated) aromatic hydrocarbons, commonly grouped as polychlorinated dibenzodioxines (dioxins, PCDDs), biphenyls and dibenzofuranes [29]. Of these chemicals, the “dioxins” are probably the best known by the public.
The number of chlorine atoms in the congeners of the different dioxins or dibenzofuranes determines the toxicity, which has led to the concept of TEQ (toxicity equivalents). The most toxic analogue is assumed to be the 4-chlorinated tetra-chloro-dibenzo-dioxin, or TCDD (Fig. 12.4.5). Concentrations in blood-lipids that cause chloracne are assumed to be in the range of 650–1,200 pg/g [30].

Chloracne is almost exclusively a symptom of systemic absorption, whereby exposure may have occurred via penetration through the skin. Exposure usually results from occupational activities or accidents, and occasionally from contamination of food or of the environment [31].

The characteristic skin lesions of chloracne are caused by changes in the keratinization of the inner linings of the hair-follicle and adjacent sebaceous gland complex. This is not very different from the very common juvenile acne, although in juvenile acne (“acne vulgaris”) an inflammatory process seems to play a role, while in chloracne lesions there is usually much less inflammation. The mechanism by which these changes in keratinization occur are largely unknown. A recent theory postulates changes in the recruitment and differentiation of the epithelial stem cells [32].

The agents causing chloracne are carcinogenic, but there is little evidence of cancer risk in humans at currently documented exposure levels [33].

12.4.4.1.2 Clinical Characteristics and Diagnosis

Chloracne should be suspected when acne-like lesions appear at unusual sites or at an age during which acne is not expected. Characteristic is the presence of open comedones, with little inflammation occur behind the ears and on the upper parts of the cheeks (Fig. 12.4.6). The whole face can be involved, as well as the neck, the shoulders, and the scrotum. The comedones may be associated with small cysts. Hyperpigmentation of the face and hypertrophy of the Meibomian glands on the eyelids have also been reported. Severely affected cases due to high exposure to the causative chemicals report non-specific symptoms of being generally unwell but most cases have no accompanying symptoms. Peripheral neuropathy has been reported.

12.4.4.1.3 General Therapeutic Outline

The first line of approach is the detection and elimination of the source of exposure to the causative chemicals. This may involve a careful inspection of the patient’s workplace or home. Chloracne tends to run a very protracted course; although the mechanism is unclear, it is probably because the “internal dose” tends to persist due to the accumulation of the causative agents in the body fat.

12.4.4.1.4 Current Established Therapies

Established therapies for acne vulgaris, even oral treatment with the retinoids isotretinoin and acitretin, have no effect [34].

12.4.4.1.5 Experimental Approaches

Oral tetracycline with UV light irradiation and topical vitamin A has limited effect [29, 35]. Persistent lesions and scars can be treated by dermabrasion or by light
cautery [36]. However, if there is a substantial dose stored in the fat tissue new lesions may continue to appear.

Another approach is to eliminate dioxins from the body either via the skin [37] or by increasing the fecal excretion by an oral non-absorbable dietary fat substitute [38].

### 12.4.4.1.6 Complications to Avoid

Local treatment of the chloracne lesions may result in persistent scarring, and the potential adverse effects of oral retinoids have been well documented. A major hazard is the failure to recognize the typical clinical picture of chloracne causing unnecessarily prolonged exposure to the causative chemicals.

### 12.4.5 Hand-Arm Vibration Syndrome; Vibration White Finger

#### Key Features

- Worker exposed to vibrating machinery [39, 40]
- Tingling and paraesthesia may precede
- White fingers precipitated by cold
- Usually asymmetric; thumbs spared

#### 12.4.5.1 Etiology and Pathophysiology

The disorder is caused by vibration transmitted through the hands to the upper limb and is caused by holding power tools, hand guided machinery, or materials being processed by machines. Occupations potentially at risk include mining, stone masonry, engineering, forestry, vehicle repair, construction, those using high speed drills, e.g., dentistry, and less obvious exposures such as the use of high-pressure hoses. The risk of developing the disorder is related to cumulative exposure to vibrations over the frequency range 4–5,000 Hz. The relative contributions of vibration frequency, magnitude, and duration are unclear. It can take from 1 month to 30 years for the disorder to manifest. Where the tool has to be gripped tightly, this increases transmission of vibration to the limb.

Evidence suggests that vibration directly induces local damage to nerves and blood vessels and in vibration white finger an increased sensitivity of vessels to sympathetic stimulation [41]. The release of endothelin-1 from damaged endothelium has been proposed as a mechanism for inducing vasospasm as has damage to perivascular nerves resulting in loss of the vasodilator effect of calcitonin gene related peptide [42]. Pathological changes include tissue oedema, arterial medial hypertrophy, and demyelinating neuropathy.

#### 12.4.5.2 Clinical Characteristics and Diagnosis

Symptoms include tingling, numbness, loss of tactile sensitivity, dexterity, and grip associated with blanching.
Occupational Dermatoses of the fingers. Arthralgia of the elbow, wrist, and hands is associated and may progress to osteoarthritis. There is also reported to be an increased risk of developing Dupuytren’s contracture. Diagnosis relies on history of exposure, presence of compatible symptoms, and exclusion of other causes. The severity is staged according to the Stockholm Workshop scale (Table 12.4.8). In general, neurological symptoms (tingling and numbness) begin before the vascular (vibration white finger).

Various tests are used to help with the diagnosis. While individual tests are not sufficiently sensitive or specific to be used alone a combination may be more useful. Assessments of vascular function include precipitation of Raynaud’s phenomenon by cold and measurement of skin temperature and finger systolic blood pressure following cold challenge. Neurological abnormalities can be assessed by measurement of thermal and vibrotactile perception thresholds. Two point discrimination and depth sense perception become impaired in more severe disease and eventually hand grip strength is reduced. Phalen’s and Tinel’s tests may be used in an attempt to exclude carpal tunnel syndrome and other provocation tests to exclude thoracic outlet syndrome.

12.4.5.3 General Therapeutic Outline

There is a consensus that workers should be removed from exposure at Stockholm workshop scale 2 or 3. At level 3 vascular or neurological symptoms are likely to be associated with a significant degree of functional impairment. After cessation of exposure, vascular symptoms tend to show reversibility but this is not universal and may be less in those with severe disease. As in other vascular disorders, smoking is an adverse prognostic factor. Environmental control by reducing exposure to cold, damp, and removal of other factors, such as drugs, that activate the sympathetic nervous system also help to alleviate vascular symptoms. Mittens should be worn, rather than gloves, to maintain hand temperature. The neuropathy appears to be less reversible.

If avoidance is not possible, a modified work routine with reduction in exposure time and instruction to grip tools lightly may slow progression.

12.4.5.3.1 Prevention

Regular monitoring in those exposed helps to control the risks of vibration exposure. This is likely to be most effective where there is also a company policy to manage exposure to vibrating machinery. Anti-vibration gloves have been shown to significantly reduce transmission of vibration to the limb compared with bare hands [43]. In the forestry industry, the use of anti-vibration chain saws has resulted in a reduction in the incidence of vibration white finger [44]. There is no known safe exposure level, although a level below 1 m/s² has been suggested as a level below which the risk is insignificant. In Europe [45], government directive entitles workers to health surveillance above 2.5 m/s² and sets 5 m/s² as a maximum exposure level over an 8-h period. An annual questionnaire review is recommended with examination of the upper limb possibly with simple provocation tests. In those with symptoms more frequent assessment should be undertaken.

Pre-existing Raynaud’s phenomenon or other medical conditions and therapy increasing vascular tone may predispose and influence an individual’s fitness to work with vibrating machinery. Similarly, the presence

<table>
<thead>
<tr>
<th>Stage</th>
<th>Grade</th>
<th>Cold induced white finger</th>
<th>Sensorineural effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>–</td>
<td>No attacks</td>
<td>Exposed</td>
</tr>
<tr>
<td>1</td>
<td>Mild</td>
<td>Occasional; finger tips</td>
<td>Intermittent numbness</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
<td>Occasional; distal finger</td>
<td>Persistent numbness; ↓ sensory perception</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
<td>Frequent; all finger; most fingers</td>
<td>↓ Tactile discrimination/manual dexterity</td>
</tr>
<tr>
<td>4</td>
<td>Very severe</td>
<td>Trophic changes of finger tip</td>
<td></td>
</tr>
</tbody>
</table>
of peripheral neuropathy and musculoskeletal disorders are relative contraindications to exposure in a pre-employment assessment.

**12.4.5.4 Current Established Therapies**

Calcium channel blockers are usually the first line of therapy although the evidence for their effectiveness is less than in Raynaud’s phenomenon. In a rat model, pretreatment with nifedipine reduced vibration induced vascular damage [46]. Most other suggested therapies are aimed at inducing peripheral vasodilatation (angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, and nitrates).

In instances where there is superimposed carpal tunnel syndrome surgery may alleviate neurological symptoms.

**12.4.5.5 Experimental Approaches**

Drugs to reduce platelet aggregation (oxypentifylline, stanzolol) and to reduce viscosity and emboli formation have been advocated in severe disease although their effect is questionable. There is a single report of the effective use of iloprost, an intravenous prostacyclin derivative, in an individual with severe disease with trophic changes [47].

**12.4.5.6 Complications to Avoid**

Failure to recognize early stages of the disease can result in progression to gangrene.

**12.4.5.7 Global Variations**

There is some evidence to support the concept that in warm climates the vascular component of hand-arm vibration syndrome may be less prevalent compared to the neurological changes.

**12.4.6 Scleroderma-Like Disorders**

Scleroderma and its treatment is discussed in Chap. 7.2. Occupational exposures can be a factor in precipitating systemic sclerosis and also in causing scleroderma-like disorders [48]. Occupational systemic sclerosis fulfills the criteria of the American College of Rheumatology and may be indistinguishable from the idiopathic disease. In the case of trichloroethylene, it has been proposed it or a reactive metabolite binds covalently to proteins such as topoisomerase I (Scl-70) stimulating an autoimmune response. Solvents and silica have also been hypothesized to stimulate production of fibrogenic proteins and growth factors such as interleukin-1, platelet-derived growth factor, transforming growth factor β, and fibronectin by protein binding and interactions with macrophages, respectively [49, 50].

In contrast, scleroderma-like disorders may be distinguished by the type of cutaneous change with more frequent involvement of the extremities, presence of morphea, fibrotic nodules, and joint contractures. Chemical toxicity may result in hepatic, renal, and neuromuscular damage. Angiosarcoma of the liver is reported. There may be isolated thrombocytopaenia and typically autoantibodies are not present. The disorder may stop or resolve following early removal from the source of exposure; consequently an awareness of potential precipitants is important. Chemicals and occupations that raise the possibility of an occupational cause are summarized in Table 12.4.9.

In addition to systemic sclerosis, silica and asbestos exposure have been linked to the development of other autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis [51].

**12.4.7 Pigmentary Disorders**

There are a variety of causes of cutaneous pigmentary change that may follow occupational as well as nonoccupational exposure (see Chap. 7.5).
Pigmentary changes more specific to occupational exposure occur when workplace materials are deposited in the skin or result in more superficial staining. Tattooing most commonly occurs when carbon in coal miners becomes impregnated in wounds resulting in a blue-black discoloration. Systemic or local absorption of metal salts in those exposed to silver, gold, mercury, bismuth, and tellurium may result in a blue or blue-grey discoloration. Skin and nails of individuals exposed to chromate in electroplating and tanning may develop a yellow tint while copper dust may cause a green-black discoloration of skin, hair, and teeth. More transient staining of the skin occurs in those exposed to dyes in the chemical industry. Yellow staining has also been reported with picric acid, nitric acid, various nitrogenous compounds, and glutaraldehyde.

Chemical leukoderma occurs when a chemical has a specific melanocytotoxic effect or the ability to suppress melanin production. Typically toxicity results from direct contact but ingestion and inhalation may be implicated. Derivatives of phenol and catechol (Fig. 12.4.7) are one of the largest group of chemicals implicated. Hydroxylation of the 4- (para) position and substitution of the 1-position (para-tert-butyl phenol, para-tert-butyl catechol and monobenzyl ether of hydroquinone) are factors that enhance toxicity. The chemicals are used as antioxidants and rust inhibitors and are found in deodorants, disinfectants, oil additives, paints, photographic, and printing chemicals, plasticizers, adhesives, and rubber. Hair dyes including p-phenylenediamine and related compounds have also been reported to cause occupational leukoderma.

The condition can be difficult to distinguish from idiopathic vitiligo. Clinically the development of coalescing macules rather than a single patch with perifollicular sparing is said to suggest chemical leukoderma. Involvement of scalp hair and ocular changes are rare and suggest idiopathic vitiligo as does the presence of other autoimmune disease. Typically changes are on the hands and forearms but more extensive changes can occur as a result of indirect contact with contaminated hands or systemic absorption. Depigmentation develops after preexisting melanin has been metabolized such that it can take several months of exposure for leukoderma to develop. Thus while depigmentation at the site of patch testing is frequent it
is not consistently found and a delayed reading at 4–6 weeks is necessary. Following avoidance there is often a degree of repigmentation centring on follicles. Limited disease and early avoidance are factors contributing to a better outcome. It is also thought that low dose exposure results in interference with melanin synthesis and reversible changes while at high concentrations the chemicals are cytotoxic resulting in permanent depigmentation.

12.4.8 Skin Cancer

The treatment of occupationally induced skin cancer is identical to that from other causes and is dealt with in Sect. 11 [54]. The majority of cases reported (vide supra) are UV-induced tumours in sun exposed workers such as agricultural workers, builders, etc., and may be associated with mutations in the p53-tumour suppressor gene. Melanoma has been associated with exposure to other sources of UV irradiation including printing lights, arc welding, and fluorescent lights.

Other causes of occupational skin cancer include ionizing radiation (radiologists; X-ray technician; dentist) and chemical exposure (workers exposed to arsenic, tar, coal, and oil distillates). Within tar, the main group of chemical carcinogens are the polycyclic aromatic hydrocarbons where exposure may be through inhalation as well as skin contact. Exposure to arsenic still occurs in glass works, copper, zinc, and lead smelting and the production of pesticides, herbicides, and semiconductors.

Table 12.4.10 Infections that may be related to occupation

<table>
<thead>
<tr>
<th>Exposure to:</th>
<th>Occupation</th>
<th>Infection</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>High humidity</td>
<td>Miners; workers in the tropics</td>
<td>Flexural intertrigo, Candida, Tinea cruris, pedis, Pitted keratolysis</td>
<td>Humidity/occlusion provides environment for infection to establish</td>
</tr>
<tr>
<td>Wet work and trauma</td>
<td>Butcher, fishmonger, abattoir workers, manual workers catering industry</td>
<td>Ecthyma, Impetigo, Viral warts, Tinea manuum, Candida paronychia</td>
<td>Minor trauma allows infection entry or to spread</td>
</tr>
<tr>
<td>Contagious human disease</td>
<td>Health care, sex industry, laboratory worker, contact sports</td>
<td>Herpes simplex, Scabies, Syphilis, AIDS, Tuberculosis</td>
<td>Close contact and skin damage facilitate transmission of human disease</td>
</tr>
<tr>
<td>Farm animals</td>
<td>Farmer, veterinarian, abattoir workers, butcher</td>
<td>Tinea, Orf, Milker’s nodule, Anthrax, Brucellosis, Erysipeloid</td>
<td>Global variation reflects exposure and extent to which infection in farm animals has been eliminated</td>
</tr>
<tr>
<td>Fish</td>
<td>Fisherman, Fish keeper</td>
<td>Erysipeloid, Fishtank granuloma</td>
<td>At sites of injury</td>
</tr>
<tr>
<td>Environment</td>
<td>Agricultural workers, Miners</td>
<td>Mycetoma, Chromoblastomycosis, Sporotrichosis</td>
<td>Inoculation by thorns and splinters esp. tropics S. Africa</td>
</tr>
</tbody>
</table>

Fig. 12.4.7 Structural similarity between several chemicals causing occupational leukoderma and tyrosine a substrate for tyrosinase in the production of melanin.
The most common tumour resulting from chemical carcinogenesis is squamous cell carcinoma. Various changes may precede the development of cancer and aid in the clinical diagnosis. In particular initial erythema and burning (tar smarts) may be followed by poikiloderma and papillomas (tar warts) that then develop into squamous carcinoma.

### 12.4.9 Infection

Infective conditions where an occupational relationship may need to be considered [55] are summarized in Table 12.4.10. Section 12.4.2 details the treatment of these disorders.

### References

45. The European Physical Agents (Vibration) Directive 2002/44/EC
12.5.1 Etiology and Pathophysiology

Wound healing is a dynamic, interactive response to tissue injury that involves complex interactions of various resident cells and infiltrating leukocyte subtypes, extracellular matrix molecules, and soluble mediators. The immediate goal in repair is to achieve tissue integrity and homeostasis [51, 67]. To achieve this goal the healing process involves three phases that overlap in time and space: inflammation, tissue formation, and tissue remodeling (Fig. 12.5.1).

During the inflammatory phase, platelet aggregation is followed by infiltration of leukocytes into the wound site. In tissue formation, epithelialization and newly formed granulation tissue, consisting of endothelial cells, macrophages, and fibroblasts, begin to cover and fill the wound area to restore tissue integrity. Synthesis, remodeling, and deposition of structural extracellular matrix molecules are indispensable for initiating repair and progression into the healing state. Cellular responses to injury involve direct cell–cell and cell–matrix interactions, as well as the indirect crosstalk between different cell populations by soluble mediators. Indeed, complex interactions between the epidermal and dermal compartment are essential. During the past decade, numerous factors have been identified that are engaged in a complex reciprocal dialogue between epidermal and dermal cells to facilitate wound repair [74]. The sensitive balance between stimulating and inhibitory mediators during diverse stages of repair is crucial for achieving tissue homeostasis following injury.

Phases of repair must occur in a proper sequence for optimal wound healing. Multiple systemic diseases and local factors can inhibit mechanisms of normal wound repair, which may lead to non-healing wounds (chronic wound = wound, which shows no tendency for healing at...
The non-healing wound is a result of an impairment in one or more of the healing mechanisms. It is essential to consider which aspect of wound healing biology has been altered when analyzing a chronic non-healing wound. For example, disturbances in inflammation will interfere with all subsequent wound healing processes. Therefore, increased or impaired inflammation may manifest itself as inadequate angiogenesis, mesenchymal cell chemotaxis and proliferation, epithelialization, wound contraction, collagen synthesis and remodeling. The factors that lead to impaired healing can be classified as systemic and local factors. Local factors include necrotic tissue, senescent cells, bacterial components, local toxins, mechanical irritation, growth factor deficiency, increased proteolytic activity, and inadequate blood supply [24, 25]. Systemic or constitutional factors are characterized by underlying internal diseases, including venous insufficiency, ischemia, rheumatological and connective tissue diseases, vasculitis, malnutrition, age, obesity, therapeutic interventions such as immunosuppressant drugs. When a therapeutic regime is discussed, each of these factors has to be critically considered and an accurate diagnosis of the factors impairing healing is a prerequisite for the successful treatment of a non-healing wound.

### 12.5.2 Clinical Characteristics and Diagnosis

Non-healing wounds have adverse effects on quality of life for the patient and are of enormous socioeconomical importance. In western countries, the incidence of...
non-healing wounds is estimated 1% with a prevalence of 3–5% in the population over 65 years of age [4]. It has been estimated that the economic burden of the European Community for treatment of wounds is about 2% of the total health care costs [45]. The incidence and prevalence of chronic wounds is rising as a result of the aging population and increased risk factors for atherosclerosis such as smoking, obesity, and diabetes.

Before deciding on a systemic or local therapy regimen, it is vital to be aware of the large differential diagnosis that lead to tissue damage and factors, which impede healing mechanisms (Fig. 12.5.2).

Furthermore, assessment of the non-healing wound is crucial and includes aspects as localization and size of the wound, wound edge characteristics, wound bed, necrotic tissue and eschar, pain, wound exudates, and surrounding skin (Tables 12.5.1 and 12.5.2). In a large portion of patients, these informations will already lead to a working diagnosis, which might be confirmed by additional objective measurements including laboratory test and instrumental investigations (Tables 12.5.3, 12.5.4, and 12.5.5). Because chronic wounds are at risk for neoplastic progression, in particular the development of squamous cell carcinoma [5, 76], or alternatively neoplasms can be “masked” by the symptom of a chronic wound, it is highly recommended to take tissue biopsies of the wound edge.

### 12.5.2.1 Impaired Healing Associated with Vascular Disease

Most non-healing wounds occur at the lower extremity and are secondary to vascular disease [65]. Chronic venous disease is responsible for approximately two-thirds of leg ulcers, whereas one-third have a mixed venous and arterial etiology. Only about 5% are due to pure arterial disease (Fig. 12.5.3).

**Ulcus cruris venosum**

- History of deep vein thrombosis
- Ankle edema worsening towards the end of the day
- Pain associated with edema
- Pain relieve with leg elevation

**Ulcus arteriosum**

- Intermittent claudication, and/or rest pain
- Pain worsened with leg elevation, pain relieve in dependent position

---

**Table 12.5.1** Typical patient’s history in venous and arterial leg ulcer

<table>
<thead>
<tr>
<th>Ulcus cruris venosum</th>
<th>Ulcus arteriosum</th>
</tr>
</thead>
<tbody>
<tr>
<td>- History of deep vein thrombosis</td>
<td></td>
</tr>
<tr>
<td>- Ankle edema worsening towards the end of the day</td>
<td></td>
</tr>
<tr>
<td>- Pain associated with edema</td>
<td></td>
</tr>
<tr>
<td>- Pain relieve with leg elevation</td>
<td></td>
</tr>
<tr>
<td>- Intermittent claudication, and/or rest pain</td>
<td></td>
</tr>
<tr>
<td>- Pain worsened with leg elevation, pain relieve in dependent position</td>
<td></td>
</tr>
</tbody>
</table>
S. A. Eming

of the disease to the point of skin lesion. In the past 20
years, a number of adjunctive factors have been investi-
gated to understand the etiology of venous ulceration,
but yet none of them completely explains the entire
pathogenetic cascade leading from venous insuffi-
ciency to skin ulceration. In 1982, Browse and Burnand [10]
observed a pericapillary fibrin deposition and speculated
that cuffs act as a barrier to oxygen diffusion and nutri-
tents. Coleridge-Smith in 1988 proposed the leukocyte
trapping theory [16, 25]. Hemodynamic changes on the
microvascular level lead to disturbed rheological condi-
tions. Blood cells are trapped in the venous microcircu-
lation secondary to venous hypertension, release toxic
metabolites, which lead to tissue damage. Furthermore,
several authors established that macrophages and neu-
trophils are the predominant cells migrating into the site
of skin chronically altered by venous stasis and leading
to severe skin damage [47]. Finally, persistence of
inflammatory cells at the wound site leads to an unre-
limited proteolytic activity, which is commonly consid-
ered the final executor of a pathogenetic chain leading to
matrix disruption, proteolysis of growth factors and their
receptors, which are essential for healing [6].

**Arterial ulceration** is caused to reduced arterial
blood supply resulting in tissue hypoxia and tissue
damage. The most common cause is atherosclerotic
disease of the medium and large-sized arteries. Risk
factors for atherosclerosis include smoking, hyperlipi-
demia, hypertension, and diabetes mellitus. Arterial
occlusion with subsequent distal tissue damage might
also occur in embolism (cholesterol, fat) and microcir-
culatory disorders (Raynaud disease, Buerger disease,
increased blood viscosity).

### Table 12.5.2 Clinical features of the most common causes of leg ulcers

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Ulcus cruris venosum</th>
<th>Ulcus arteriosum</th>
<th>Diabetes mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
<td>Gaiter area of the leg; malleolar regions</td>
<td>Acren (toes, heels), pressure sites</td>
<td>Plantar (under the halux, I/V metatarsal heads, heel); foot margins</td>
</tr>
<tr>
<td><strong>Surrounding skin</strong></td>
<td>Pigmentation secondary to hemosiderin; lipodermatosclerosis (“inverted champagne bottle”)</td>
<td>Change of atrophy (brittle, thin hairless skin); toenails thicken;</td>
<td>Callus, changes of atrophy; dry skin</td>
</tr>
<tr>
<td><strong>Ulcer morphology</strong></td>
<td>Fibrinous granulating ulcer bed; irregular, gently sloping edge; exudate</td>
<td>Pale, non-granulating, necrotic ulcer bed; punched out, well demarcated edge</td>
<td>Punched out edge; deep, non-granulating ulcer bed; blister under callus</td>
</tr>
<tr>
<td><strong>Other typical clinical findings</strong></td>
<td>Varicosity; atrophie blanche; ankle edema; stasis dermatitis; lymphedema; poor calf-muscle function</td>
<td>Gangrene; absent pulse in the A dorsalis pedis and tibialis posterior; reduced capillary refill time; cold, cyanotic skin</td>
<td>Neuropathy (sensoric, motoric, autonomic) with decreased sensation; infection; cocked-up toes, prominent metatarsal heads</td>
</tr>
</tbody>
</table>

### Table 12.5.3 Instrumental investigation to assess major causes of leg ulcers

<table>
<thead>
<tr>
<th>Ulcus cruris venosum</th>
<th>Ulcus arteriosum</th>
<th>Diabetes mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duplex ultrasound</td>
<td>Hand held doppler to measure ABPI</td>
<td>Monofilaments and tuning fork to assess sensation</td>
</tr>
<tr>
<td>Photoplethysmography</td>
<td>Duplex ultrasound</td>
<td>Angiography</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X-ray, NMR or bone scan to exclude osteomyelitis</td>
</tr>
</tbody>
</table>

### Table 12.5.4 Laboratory screening tests for chronic wounds associated with vasculitis

- Erythrocyte sedimentation rate
- Differential blood count
- Kidney and liver function
- Antinuclear antibodies
- Rheumatoid factor
- Complement (C3, C4)
- Paraproteins (cryoglobulins, cyrofibrinogen)
- p-c-ACNA
- Urine analysis for proteinuria, haematuria, cylindruria

### Table 12.5.5 Laboratory screening tests for chronic wounds associated with clotting disorders

- Activated partial thromboplastin time
- Prothrombin time
- Thrombin time
- Factor V (Leiden) mutation (906R → 906Q)
- Factor II (prothrombin mutation 20210G → 20210A)
- Antithrombin III
- Protein C and protein S
- Lupus anticoagulant
- Anticardiolipin antibodies
Diabetes mellitus is the most common metabolic disease associated with impaired wound healing. Currently, it is not clear to which extent impaired healing is due to direct effects of insulin deficiency or its sequelae including hyperglycemia, hyperlipidemia, or obesity. The most common clinical picture of impaired wound healing associated with diabetes is the diabetic foot ulcer (Fig. 12.5.5).

Among diabetic patients, 2–3% will develop a foot ulcer each year, 15% will develop a foot ulcer during their lifetime [60]. Skin ulceration and healing impairment is caused by the combination of several intrinsic factors (neuropathy, vascular disease, other complicating systemic effects due to diabetes) and extrinsic factors (wound infection, callus formation, and excessive mechanical pressure) [27]. In addition, phenotypic and functional cellular abnormalities of wound fibroblasts, endothelial cells, and inflammatory cells have been described, which might be responsible for the healing impaired situation. Furthermore, Necrobiosis lipoidica, a granulomatous dermatitis of yet unknown pathogenesis, can be associated with diabetes mellitus and has a propensity to ulceration [28]. Characteristically, such ulcerations are localized at the pretibial region, slow healing, painful, and often complicated by infection.

**12.5.2.2 Impaired Healing Associated with Increased Pressure**

Pressure ulcers (Decubitus) are areas of tissue necrosis caused by unrelieved pressure to soft tissue compressed between a bony prominence and an external surface for a prolonged period of time. The most common bony prominences involved are the sacrum, ischial tuberosities,
greater trochanters, heels, and lateral malleoli. The four major etiologic factors involved in the development of pressure ulcers are pressure, shearing forces, friction, and moisture. Decubitus can be divided into four stages, depending on the extent of tissue damage: stage I, non-blanchable erythema; stage II, partial thickness loss of skin layers (blisters, abrasion); stage III, full thickness skin loss exposing subcutaneous fat; stage IV, exposed muscle or bone (deep ulcer or necrosis).

12.5.2.3 Impaired Healing Associated with an Altered Immune Response

Increased and persistent inflammation can lead to skin ulceration and impair healing. *Pyoderma gangrenosum* (Fig. 12.5.6) is a classical proinflammatory disorder associated with skin ulceration and impaired healing. Underlying pathomechanisms are still not clear. More than 50% of cases of *Pyoderma gangrenosum* have an antecedent or coincident associated disease or condition, including ulcerative colitis, Crohn’s disease, chronic hepatitis, rheumatoid arthritis, lupus, or malignancies [12]. In the other 50% of *Pyoderma gangrenosum* cases, no associated disease can be identified and they are considered idiopathic. The lower extremities and trunk are the most common sites.

*Fig. 12.5.5* Neuropathic ulcer associated with diabetes mellitus; repetitive mechanical forces of gait lead to callus; note, callus represents the most important preulcerative lesion in the neuropathic foot

*Fig. 12.5.6* *Pyoderma gangrenosum*; typical pustules at the disease onset (*left*) and extensive ulceration (*right*) during disease progression
of skin ulcers. The diagnosis of pyoderma gangrenosum is primarily clinical as there are no specific laboratory or histologic features. History of one of the mentioned underlying diseases supports the diagnosis. Pathergy occurs in 25–50% of cases. Typically, the lesions begin as painful pustules, with rapid development of necrosis and ulceration. The ulcer has a characteristic erythematous or violaceous overhanging edge. The wound bed is purulent and may extend to muscle. A recent article mentioned Pyoderma gangrenosum being overestimated by 10% due to misdiagnosis of many cases [73].

*Vasculitis* denotes a heterogenous group of diseases characterized by inflammatory vessel damage. Several subdivisions can be made, based on vessel size (large vessel, medium-sized, small vessel), cell infiltrate (polymorphonuclear, mononuclear, granulomatous), or clinical presentation [29]. Cutaneous vasculitis may present as purpura, erythema, noduli, bullae, or skin infarction leading to ulceration. Cutaneous ulceration is usually caused by medium- to small-sized vessel leukocytoclastic vasculitis. Cutaneous necrotizing vasculitis can be idiopathic or associated with a number of disorders and conditions: infection (hepatitis, streptococci, mycobacteria), inflammatory diseases (rheumatoid arthritis, systemic lupus erythematosus), drug intake, malignancies (lymphoma, carcinoma). *Livedo vasculopathy*, also known as livedo vasculitis, is a chronic, recurrent, ulcerative skin disease with typical clinical features such as atrophy blanche, painful superficial leg ulcers, and persistent livedo racemosa. Histologic features include intraluminal thrombosis of dermal blood vessels and a mild perivascular lymphocytic infiltrate. The pathogenesis of *Livedo vasculopathy* is not fully understood, and it has been described as idiopathic, associated with immune complex associated diseases, and a result of dermal blood vessel occlusion due to altered local or systemic control of coagulation [35].

### 12.5.3.4 Additional Differential Diagnosis

Many types of cancers, including metastases, can present with skin ulceration, including the most common form of skin cancers, basal cell carcinoma and squamous cell carcinoma (Fig. 12.5.7).

Squamous cell carcinoma may develop in longstanding chronic wounds associated with burns, scares, or venous disease [5, 76]. Clinical features indicative of neoplasm include resistance to therapy, elevated, and frequently a rolled edge. Therefore, to exclude malignancy of a chronic non-healing lesion a histological evaluation is mandatory.

*Claciphylaxis* is characterized by progressive vascular calcification, and ischemic necrosis of the skin and soft tissue. The most common cause of metastatic calcification is chronic renal failure and consequent disturbances of the solubility product of calcium and phosphate. Molecular mechanisms how a disturbed calcium and phosphate metabolism contribute to tissue necrosis are still unclear.

Several pharmacologicals can lead to skin ulcers with impaired healing. Hydroxyurea, used to treat myeloproliferative disease, may cause painful, shallow, ulcers at the lower leg over the medial malleolus or lateral aspect of the foot (Fig. 12.5.8). Healing is usually only achieved when the drug is discontinued. Furthermore, immunosuppressant therapies can lead...
to impaired healing, emphasizing the importance of the inflammatory response for efficient healing. The most classical example is glucocorticoid-induced impaired healing.

### 12.5.3 General Therapeutic Outline

Once the contributory factors of the impaired wound healing situation have been identified, wound treatment can be initiated. In most cases, the underlying cause interfering with wound healing is multifactorial, therefore it is mandatory to choose an interdisciplinary treatment approach, which considers the treatment of systemic and local factors (Fig. 12.5.3). Specialized wound-care centers offer a comprehensive program, which is based on a standardized interdisciplinary diagnosis and therapy thus aiming at effective, systematic, and ultimately cost-reductive wound management. Ideally, procedures follow guidelines integrated in the national health care system [34].

Correcting the underlying systemic disease of impaired healing can be very variable as the causes are manifold associated with wound healing disorders. For example, diseases of the vascular system associated with chronic wounds require restoration of a functional vascular system. Impaired healing associated with diabetes mellitus is based on the normalization of hyperglycemia and hyperlipidemia and their sequelae. Treatment for pyoderma gangrenosum or vasculitis is in general based on a systemic immunosuppressive therapy.

The goal of local wound care is to modulate the hostile environment of the chronic wound with the aim of restoring a biochemical environment that stimulates endogenous healing mechanisms. In most cases, it is not possible to apply the principles of acute wound healing to chronic wounds without considering the biochemical environment present in the latter. Chronic wounds have complex, inflammatory nature and produce substantial amounts of exudates, which interfere with the healing process and the effectiveness of therapeutic products adequate for acute wounds. A typical feature of non-healing wounds is a prolonged inflammation and heavy bacterial burden, leading to excessive levels of proteases. An unbalanced proteolytic environment results in increased breakdown of the extracellular matrix, growth factors and their target cell receptors, preventing granulation tissue formation and reepithelialization [32, 33, 46]. The principle of local modern wound therapy is to convert the hostile chronic wound microenvironment in an environment, which is conductive for repair. This process is based on optimal wound bed preparation which is achieved by a phase-adapted treatment regime (Fig. 12.5.9). The ultimate aim is to ensure formation of healthy granulation tissue leading to complete wound closure, either naturally through epithelialization or through skin products or grafting procedures. A phase-adapted treatment regime includes debridement, induction of granulation tissue formation, and stimulation of epithelialization.

**Fig. 12.5.9** Conversion of a chronic, non-healing microenvironment hostile for repair into a healing microenvironment. A phase-adapted treatment regime includes wound bed preparation consisting of debridement and induction of granulation tissue formation, which activates epithelialization.
12.5.4 Current Established Therapies

12.5.4.1 Treatment of Systemic Disease

12.5.4.1.1 Restoration of Functional Vascular System

Diseases of the vascular system are the most frequent causes of chronic wounds. These include venous or arterial insufficiency. Normalization of blood supply and blood drainage is mandatory to induce tissue repair.

The main goal of therapy in arterial ulcers is the re-establishment of an adequate arterial supply. Patients should be referred to a vascular surgeon for assessment and revascularization by angioplasty or bypass surgery. Although not unequivocally conclusive, additional non-surgical therapies are available to improve perfusion of peripheral vascular beds. These strategies are considered as adjuvant agents and include systemic therapy with Pentoxifylline, Illoprost, calcium antagonists, aspirin, or clopidrogel [13, 15]. Good clinical evidence suggests that Cilostazol, a phosphodiesterase inhibitor, improves pain-free and maximal treadmill walking distance [37]. In addition, several propionyl l-carnitines are currently being explored for the treatment of claudication and arterial leg ischemia [37].

The mainstay of therapy in venous insufficiency and the prevention of skin ulceration is to normalize venous hypertension. The most common and practical therapy is compression, and if possible combined with leg elevation above the heart. Although the optimal pressure necessary to overcome venous hypertension is not well defined, it is generally agreed on that graded compression, with greatest compression (about 40 mmHg) at the ankle, tapering off to lower pressure (about 18 mmHg) below the knee, effectively increases the limb hydrostatic pressure and concomitantly reduces the superficial venous pressure. Various compression bandage systems are used. These include the single and multi-layer elastic bandage system, short stretch bandage, and elasticated tubular bandage. Compression with pneumatic devices can be used in patients with excessive edema. Patients should be warned to remove the compression if they notice any side effects (pain, numbness, color change of toes) and seek medical advice.

In addition to compression, venous hemodynamic correction can be performed by eliminating insufficient veins either by sclerotherapy or by superficial vein surgery [69]. While it is still controversial if the addition of superficial venous reflux correction by surgery has positive effects in reducing ulcer healing time, there is wider agreement in the associated reduction of recurrences [7]. In addition, a recent systematic review that evaluated the overall rates of clinical outcomes in patients with chronic venous disease concluded that surgery, with or without saphenous ablation, leads to an 88% chance of ulcer healing and a 13% chance of recurrence [79].

Although with little clinical evidence, several pharmacologicals (Pentoxifylline, Prostaglandins, Stanozolol) have been proposed as an adjunct to reduce consequences of increased venous hypertension and hence to improve healing or to reduce recurrence of venous ulcers [17, 41].

12.5.4.1.2 Correction of Metabolic State

Diabetes mellitus is the most common metabolic disease associated with impaired wound healing. Studies indicate that the incidence of both vascular and neurological complications of diabetes can be significantly reduced when blood glucose concentrations are maintained to normal levels [14, 71]. Therefore, correction and consequent monitoring of metabolic abnormalities by insulin or anti-diabetic therapy is mandatory for any wound healing therapy [27].

Claciphylaxis is characterized by progressive tissue necrosis. Although it remains still unclear how a disturbed calcium/phosphate metabolism and hyperparathyroidism contribute to excessive tissue necrosis, low-calcium dialysis and parathyroidectomy are recommended therapies aiming at normalizing the calcium/phosphate metabolism and hence preventing tissue necrosis.

12.5.4.1.3 Normalization of Immune Response

Inflammatory disorders can lead to skin ulceration and impair healing. Treatment of pyoderma gangrenosum has to consider a potential underlying systemic disease and the severity of the disease. Immunosuppression, the mainstay of treatment however is mostly empirical and has been diverse. A recent
evidenced-based review of the literature and evaluation of recommendations for pyoderma gangrenosum treatment concluded that therapeutic efficacy of systemic treatment with corticosteroids and cyclosporine is best documented in the literature for disseminated as well as for localized disease and should be considered first-line therapy [61]. As such, prednisolone 1–2 mg/kg/day can be used as initial therapy. When steroid treatment has to be reduced because of side effects azathioprine (2–3 mg/kg/day) can be used. In cases that do not respond to this treatment alternative therapeutic procedures have been investigated such as mycophenolate mofetil or tacrolimus [49]. Recently, good outcomes have been reported for treatments based on TNF-α blockade [9]. Sulfa drugs (sulfadiazine) or dapsone can be used in less-aggressive ulcers [8, 39].

Ulceration and wound healing disorders are a common feature of many connective tissue diseases associated with an altered immune response. For example, skin ulceration develops in up to 10% of patients with rheumatoid arthritis [72]. Ulceration is usually of rapid onset or enlargement and associated with deterioration of the rheumatoid disease. Therapy includes systemic immune suppression including steroids, MTX, or azathioprine [52]. Recently, refractory and recurrent skin ulceration in a young patient with seronegative rheumatoid arthritis was successfully treated with anti-TNF-α therapy [38].

As outlined above cutaneous vasculitis is often associated with an underlying systemic disease which has to be identified prior treatment. Skin ulceration due to cutaneous vasculitis often requires immunosuppressive therapy including corticosteroids, azathioprine, or cyclosporine.

12.5.4.2 Local Treatment

12.5.4.2.1 Debridement

Regardless of the underlying systemic disease, initially, all chronic wounds should be cleaned of necrotic and fibrinous debris to allow the formation of granulation tissue and adequate epithelialization (Figs. 12.5.9 and 12.5.10).

Necrotic tissue provides a mechanical barrier for granulation tissue to form, for migrating keratinocytes, for diffusion processes of local applied medications, and it offers a stimulus for perpetuating inflammation and a substrate for bacterial growth. Debridement can be carried out mechanically, autolytically, or surgically (Table 12.5.6). A multicenter, randomized, double blind, placebo-controlled study provided convincing evidence that enzymatic treatment does not lead to efficient wound debridement and is not considered an adequate method of wound therapy (data not published). Wet-to-dry saline dressings have been used for

---

**Fig. 12.5.10** Chronic ulcus cruris venosum: example of a topical treatment regimen
decades for efficient wound debridement. For this method simple wet and wide meshed gauze is applied to a wound and allowed to dry. Recently, also more user-friendly superabsorbent polymers have been developed and follow the wet-to-dry treatment. However, the wet-to-dry method can be painful and can strip away newly formed epithelium. Wounds heavily colonized with bacteria need to be treated antiseptically in order to prevent the development of an infection. Numerous local antimicrobial agents are available including povidone-iodine, polyhexanid, octenidin, chlorhexidine, silver, and antibiotics (Table 12.5.6). However, wound treatment with all these local antimicrobial agents should be weighed against the risk of toxic effects of these agents, as well as allergic reactions. Therefore prolonged use of any local agent should be avoided. Hydrogels are gel-like sheets that are non-adhesive, absorbent and are effective in desloughing wounds. Autolytic debridement refers to the natural self-clearance of debris in the wound bed by phagocytic blood cells and endogenous proteolytic enzymes. This process can be promoted and enhanced by maintaining a moist environment using occlusive dressings.

Wounds resistant to conservative debridement methods require a surgical debridement. A surgical debridement can be accomplished under local anesthesia using a curette or scissors and forceps or in the operating room under general anesthesia using a dermatome. The latter technique has been described as “shave therapy” when the complete ulcer and the surrounding lipodermatosclerotic tissue are removed extensively [66]. A reemerging technique of debridement is the use of maggots also named biosurgery [55]. Usually, sterile larvae of Lucilia sericata are used, which produce potent enzymes to digest necrotic material without harming surrounding healthy tissue. Maggots’ components also appear to combat clinical infections. Pain and psychological discomfort may be issues for some patients and nurses.

### 12.5.4.2.2 Induction of Granulation Tissue

**Wound dressings**

Once the wound is clean of fibrinous, fibrotic, and necrotic tissue local agents and dressings should be used to improve healing. A large variety of wound dressings is currently available, which require a phase-adapted application based on their dressing-specific properties (Table 12.5.7). However, it is still unclear whether particular dressings aid healing of chronic wounds and which might be the underlying mechanisms. Most dressings support wound healing by acting as a barrier between the wound and the environment, preventing drying of the tissue [57]. Currently, only few dressings might actually interfere with cellular and molecular mechanisms of the hostile chronic wound microenvironment that counteract healing mechanisms.

Since Odland first demonstrated that a blister healed faster if left intact [56], and Winter showed that in occluded wounds reepithelialization occurs more quickly in the moist environment [75], a variety of synthetic occlusive dressings have become available. Numerous animal studies and clinical trials have demonstrated the beneficial effects of occlusive dressings on wound healing [18, 75]. In acute wound models, different mechanisms of actions are discussed. One attractive hypothesis is that a variety of growth factors accumulates in the wound fluid that can modulate tissue

<table>
<thead>
<tr>
<th>Table 12.5.6 Approaches for wound debridement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical debridement</td>
</tr>
<tr>
<td>Surgical debridement</td>
</tr>
<tr>
<td>Antimicrobial wound dressings/agents</td>
</tr>
<tr>
<td>– Silver dressings</td>
</tr>
<tr>
<td>– Hydrogel</td>
</tr>
<tr>
<td>– PVP-iodine, Octenidin, Polyhexanid, Chlorhexidine</td>
</tr>
<tr>
<td>Maggot therapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 12.5.7 Therapeutic approaches to induce granulation tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound dressings</td>
</tr>
<tr>
<td>– Alginates</td>
</tr>
<tr>
<td>– Hydrocolloids</td>
</tr>
<tr>
<td>– Foam dressings</td>
</tr>
<tr>
<td>– Hydropolymer dressings</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>– Hyaluronic acid</td>
</tr>
<tr>
<td>– Growth factor (PDGF-BB)</td>
</tr>
<tr>
<td>Cell based treatments</td>
</tr>
<tr>
<td>– Keratinocytes</td>
</tr>
<tr>
<td>– Skin equivalents</td>
</tr>
<tr>
<td>Device</td>
</tr>
<tr>
<td>– Negative pressure wound therapy</td>
</tr>
</tbody>
</table>
repair. Additionally, the pO$_2$ is low under occlusive dressings, suggesting that the expression of hypoxia-regulated cytokines, such as VEGF, is increased. This would explain the increased angiogenesis which has been observed using hydrocolloid dressings.

A variety of different dressings, which consider the concept of moist wound healing have become available (Table 12.5.7). *Hydrocolloids* are gas-permeable, absorbent dressings composed of three-dimensional networks of hydrophilic polymers made from carboxymethylcellulose, polysaccharides, gelatin, or pectin and a polyurethane outer coating. They adhere to the skin surrounding the wound, thereby creating an occlusive milieu. They are easy to use and cost effective as they can remain on the wounds for several days. Disadvantages of hydrocolloids are that the occlusion can result to an unpleasant odor and can sometimes stimulate excess formation of granulation tissue. *Alginates* are biodegradable products derived from alginate acid, which is extracted from brown algae and processed into calcium alginate. In contact with wound exudate, insoluble calcium alginate turns into soluble sodium alginate through ion exchange. This initiates swelling associated with a great fluid absorption capacity. *Foam dressings* are microporous dressings manufactured from polyurethane foam. One side has a hydrophilic, soft surface that absorbs wound exudate. The other side is hydrophobic and inhibits leakage of exudate through the dressing. Foam dressings provide a moist healing environment and are not adherent. Furthermore, the role of *hyaluronic acid* in wound healing has been evaluated. It has been demonstrated that hyaluronic acid is present in a variety of tissues and plays a vital role in many biological processes critical in the tissue repair response, including tissue hydration, proteoglycan organization, cell differentiation, and angiogenesis. Several animal and clinical studies could demonstrate that the local application of hyaluronic acid has a beneficial effect on the wound healing process and the compound has been formulated into biomaterials for wound healing applications. These products have been shown to have a significant effect on granulation tissue formation and reepithelialization.

Growth Factors

Because of the pivotal properties of growth factors, the hypothesis that their local application to the wound site might accelerate the process of wound repair was tested and confirmed in a wide variety of experimental animal models [74]. However, despite intense efforts in more than a decade, the clinical promise of growth factors in tissue injury application has yet to be achieved [30]. A major concern of growth factor therapy in tissue repair is the effective delivery of these polypeptides into the wound site that promotes healing of the injured tissue. Introduction of growth factor genes into cells participating in the healing response might be an ideal mechanism for drug delivery by local, autologous expression (see Experimental approaches).

The only recombinant human growth factor currently licensed for commercial use in diabetic foot ulcers is Platelet Derived Growth Factor-BB (rhPDGF-BB, Becaplermin, Regranex gel). A multicenter, double blind randomized controlled trial in patients with chronic diabetic foot ulcers showed local PDGF to be superior to placebo in promoting healing [63, 68]. Its effectiveness was further enhanced when used in conjunction with surgical debridement of the wound bed, emphasizing the importance of good basic wound care.

**Cell-Based Treatments**

When skin defects are too large to heal by secondary intention, skin grafts and cell based treatments may be used (Table 12.5.8). Split-thickness skin grafts are most commonly used for the treatment of chronic wounds. These grafts are harvested from the thigh using a dermatome. Usually meshed grafts are used to allow wound fluid to escape through graft interstices. An old-fashioned but efficient and simple method for skin grafting in ulcer therapy is based on punch biopsy grafts. For this method, superficial punch biopsies are harvested usually from the thigh and placed dermis-side down on the ulcer bed spaced several millimeters apart [53].

During the past decades, numerous efforts have been directed toward the development of a skin substitute

---

**Table 12.5.8 Approaches to promote wound closure**

- Pinch grafts
- Split thickness skin graft
- Epidermal graft
- Skin equivalents(Apligraf®, Dermagraft®)
- Reconstructive surgery
- NPWT
with qualities similar to native skin and these substitutes have been investigated to aid healing of chronic wounds [40]. Studies included the development of “tissue therapies” using auto- and allogeneic materials in bioengineered human skin equivalents. Initially the work on skin substitutes focused on two separate areas, restoration of the epidermis and the development of a dermal analog. Rheinwald and Green demonstrated that epidermal keratinocytes could be cultured in vitro using a feeder layer of murine fibroblasts [62]. Based on this discovery, companies started a service to produce cultured grafts of autologous and allogeneic epidermal keratinocytes. These grafts have been successfully used for the coverage of large areas, including wounds in third-degree burns, epidermolysis bullosa, pyoderma gangrenosum, and chronic wounds [2, 59, 70]. Although, to date, the literature on autologous cells allows no conclusive statement concerning the persistence of the transplanted cells, it is well documented that allografts do not result in permanent take. Several clinical studies demonstrated that both allogeneic and autologous grafts had a beneficial effect on chronic wounds refractory to conventional therapy. Although the cells are eventually lost from the graft site, it is believed that the cells accelerate the healing process by providing an occlusive covering that sustains the synthesis and secretion of growth factors.

Nevertheless, the performance of these thin epidermal grafts, which lack a dermal component, has not always been optimal. Others have developed and clinically tested various dermal analogs, the first of which was a porous collagen-glycosaminoglycan (C-GAG) matrix [11, 36]. Although the clinical performance of this dermal analog was acceptable, it lacks a viable epidermis and must be covered with a thin split-thickness autograft. Later efforts have concentrated on developing a composite graft of cultured keratinocytes seeded onto a dermal analog so that both epidermal and dermal components are supplied. Composite grafts have been produced with keratinocytes seeded onto various dermal analogs, including C-GAG matrices, fibroblast-contracted collagen lattices, polyglactin mesh, and an acellular dermis. Although most of these composite grafts have been applied and tested in third-degree burn patients, some composites have been applied successfully for the treatment of chronic wounds including leg ulcers, decubitus, and diabetic wounds.

In addition, a skin equivalent with an epidermal layer of cultured allogeneic keratinocytes and a dermal analog of cultured allogeneic fibroblasts in a collagen gel was developed, as a product known as Apligraf® [20, 58]. Because of the immunologic mismatch, engraftment of allogeneic cells is not permanent, but these grafts can provide temporary coverage that promotes wound healing. Apligraf® contains only fibroblasts and keratinocytes, lacking two of the main targets for rejection of skin allografts, namely, endothelial cells and antigen-presenting Langerhans cells. The immune reaction to such grafts is not expected to be as great as the response to typical cadaver allografts. A clinical study of 293 patients with chronic venous ulcerations was randomized to receive Apligraf® or a control compression dressing [26]. Apligraf®-treated wounds showed a statistically significant healing success rate (63% compared to 49%) and less time to complete wound closure (61 days compared to 181 days) over the control. No symptoms or signs of rejection occurred in response to treatment with Apligraf®, and no specific immune response was detected in vitro to bovine collagen or to alloantigens expressed on keratinocytes or fibroblasts. Different mechanisms of Apligraf® action are discussed: stimulation of healing by cellular and matrix components of Apligraf®, with epithelialization proceeding from the edge of the wound and from islands of epithelium in the wound bed; biologic effects of occlusion, with stimulation of new skin tissue formation: graft take with vascularization, integration, and eventual remodeling over time. However, despite these encouraging results, one need always to consider the potential of transmitting diseases when using allogeneic materials.

Furthermore, clinical trials with a product named Dermagraft® have been performed for the treatment of diabetic foot ulcers. Dermagraft® is composed of allogeneic neonatal fibroblasts derived from fetal foreskins grown in vitro on a bioabsorbable polyglactin mesh. Following transplantation over time the polyglactin mesh is hydrolyzed and is replaced by collagen, fibronectins, and glycosaminoglycans. A clinical study evaluating the use of Dermagraft® on diabetic ulcerations demonstrated that wounds treated weekly for 8 weeks with Dermagraft® healed faster than control wounds both to 50% and 100% closure [19, 31]. There were no adverse events associated with the Dermagraft® application and the hydrolysis of the polyglactin mesh; however, the control group healing rate was lower than expected for an adequately off-weighted, well-perfused, non-infected ulceration.
Negative Pressure Wound Therapy (NPWT)

NPWT is a non-invasive healing technique that has emerged over the past years as a treatment option for a wide range of complex, acute, and chronic non-healing wounds. This therapy is based on the delivery of subatmospheric pressure through a specialized pump, which is connected to a resilient, foam-surface dressing covered with an adhesive drape to maintain a closed environment. A technical system that is most often used to deliver NPWT is the VAC Therapy System (KCI, San Antonio, TX, USA). The clinical evidence supporting the use of NPWT is based largely on clinician perception, case series, publications but an overall low amount of evidence [23]. Recently, a multicenter, randomized controlled trial on chronic diabetic foot wounds supported the effectiveness of this method to promote healing in complex chronic wounds [1]. Cellular mechanisms how NPWT promotes the healing response are speculative; it is hypothesized that the negative pressure removes excess wound fluid from the extravascular space, leading to improved peripheral blood flow, local oxygenation and hence formation of granulation tissue. High costs and patient compliance may be issues of concern in some cases.

12.5.4.2.3 Induction of Reepithelialization

Currently, there is no product on the market, which specifically targets epithelialization. However, a healthy granulation tissue, free of scab is essential for an efficient reepithelialization and products, which promote granulation tissue formation, might indirectly promote restoration of the epidermis. Furthermore, a moisture wound environment is considered to promote reepithelialization. Thin, transparent adhesives made of polyurethane are vapor-permeable and are recommended for superficial wounds as they keep a moist wound environment and prevent the wound from desiccation. Alternatively, superabsorbent polymers, which are capable to bind wound exudate in exchange for Ringer’s solution work excellent to keep the wound clean and moist.

12.5.5 Experimental Approaches

Current limitations in the treatment of chronic wounds are due to the limitation of knowledge of molecular mechanisms hindering repair, in particular in the chronically diseased situation. Therefore, the success of novel therapies depends fundamental on a more comprehensive understanding of the underlying pathomechanisms and correction of pathogenic factors. Advances in molecular/cellular biology and material sciences have broadened research, and it is expected that those findings lead to the development of enhanced methods for treating tissue defects and healing disorders (Table 12.5.9).

Effectiveness of therapeutic strategies for the local treatment of chronic wounds is based on the delivery of a drug or protein that promotes healing of the injured tissue. A critical issue to address is the development of strategies aimed at optimizing the delivery of therapeutic factors to maximize their efficacy at the wound site. A molecular genetic approach in which genetically modified cells synthesize and deliver the desired factor (e.g., growth factor) in a time-regulated manner may be a powerful means to overcome the limitations associated with the local application of therapeutic proteins. In various animal models, different delivery technologies for gene transfer applied in tissue repair have been investigated and have been successfully applied to ex vivo and in vivo gene therapy [22, 42, 54]. Despite the fact that in vitro gene transfer strategies have been proven to be controllable, safe, and successful in various experimental models of tissue repair, so far only in vivo gene transfer approaches have reached clinical application for wound repair. At present, a Phase I clinical trial evaluating the safety and potential clinical utility of local applications of a gene for PDGF-B contained within an E1 deleted adenoviral vector is being undertaken (www.clinicaltrials.gov) [50]. Furthermore, a Phase II clinical trial investigating the overall safety and
12.5 Wound Healing

clinical outcome of a hepatocyte growth factor (HGF) plasmid vector gene therapy approach in peripheral vascular disease is taking place; evaluation includes reduction of amputation and mortality, wound healing, rest-pain reduction and improvement in subject’s ability to function without adverse consequences on quality of life (www.clinicaltrials.gov).

Advances in the field of biomaterial science and protein engineering are expected to contribute to the development of novel therapeutics in tissue repair. For example, the development of protease resistant key growth factors might circumvent a major pathomechanism of chronic wounds, which is the unbalanced proteolytic activity [46, 64]. Moreover, growth factors engineered for binding to extracellular matrix molecules have been shown to augment their biological activities for repair [48]. This approach not only uses the extracellular matrix as carrier, but also mimics the natural interactions between growth factors and extracellular matrix, which appears to be crucial for physiological growth factor action.

Recent advantages in stem cell biology are promising breakthroughs for the development of novel strategies for the treatment of chronic wounds [43]. There is great interest in delivery of stem or progenitor cells, either applied locally or recruited from the circulation. Preliminary work suggests that locally applied autologous bone-marrow derived cells promote the healing of therapy resistant chronic wounds [3]. Furthermore, recruitment of CD34+ cells from the circulation has shown promise in ischemic limbs [44]. However, stem cell therapy still poses many questions regarding timing of stem cell application, stem cell survival, and differentiation within the hostile chronic wound environment, and potential side effects.

12.5.6 Complications to Avoid

- Never start the therapy without a clear diagnosis of impaired healing.
- Chronic wounds require a histological analysis to exclude a malignancy.
- Patients with chronic wounds are particularly susceptible to contact dermatitis related to local therapies and require allergic testing.

12.5.7 Global Variations

In most countries of the western world disturbances in tissue repair and chronic wounds are recognized as clinical problem with significant socio-economical impact. Nevertheless, in Europe and the US wound management receives still a low priority in academic medical teaching programs. Information about pathophysiology, diagnosis and therapy of difficult to heal wounds is predominantly based on experience supplied by specialists, who obtained their knowledge in postgraduate courses for dermatologists, physicians in internal medicine or surgeons. Often the organization of these courses is left solely by the industry. In most European countries patients with chronic wounds are currently treated by non-specialist medical staff, who have for example little understanding about wound bed preparation or similar wound management approaches. Furthermore, insurers seldom provide reimbursement for new wound-care products or treatments and therefore the field of advanced wound management is limited. In the UK, wound management education for nurses is more advanced with respect to other countries such as Germany or France, and are the principal health care professionals involved in the care of leg ulcers. It is
hoped that dermatology in Europe and the USA in its collaborative effort with other clinical and basic science-oriented disciplines will develop a solid concept to further improve preventive and therapeutic strategies to manage difficult-to-treat chronic wounds in a cost-effective way.

References

63. Robson MC, Payne WG, Garner WL, Biundo J, Giacalone V, Cooper D et al (2005) Integrating the results of Phase IV (post-marketing) clinical trial with four previous trials reinforces the position that Regranex gel 0.01% is an effective adjunct to the treatment of diabetic foot ulcers. J Appl Res 5:35–45
A
Abacavir, 321–324
Abatacept, 34, 36
Acetate
cromadione acetate, 367
cyproterone acetate, 363, 367
Acid
cromic acid, 719
diethylenetriamine penta-acetic acid, 723
hydrochloric acid, 719
hydrofluoric acid, 719, 720
nitric acid, 732
sulfuric acid, 719
Acitretin, 78, 80–81, 83
Acne, 78–81, 83
aestivalis/Mallorca acne, 369
conglobata, 361, 363, 367, 369
cosmetica, 363
excoriated acne (acné excoriée des jeunes filles, picker’s acne), 369
fulminans, 360–364
pomade acne, 362
preadolescent (childhood, infantile or neonatal) acne, 361
steroid-induced acne, 369
tarda, 361
tropical acne, 361
venenata, 362
vulgaris, 359–362, 366, 367
Acquired bilateral nevus of Ota-like macules (ABNOM), 531–532
Acquired hyperostosis syndrome (AHYS), 363
Acrylates, 724
Actinic keratoses (AKs), 107, 609–610
Active vitamin D3, 195–197
Acute generalized eruptive pustulosis (AGEP), 303–305
Acute graft-versus-host-disease (aGVHD), 433–439
Acute miliary tuberculosis (AMT), 141
Acute viral infections, 324
Acleclovir, 159, 678
Adalimumab, 195, 201, 460
Adapalene, 79, 81, 364–366
Adenal androgen dehydroepiandrosterone sulfate (DHEA-S), 360, 361
Adeno-associated virus (AAV), 483
Adenosine deaminase (ADA), 577
Adenoviral vector, 748
Adult-onset Still disease (AOSD), 349–351
Adverse drug effects, 21
Aging, 445
AIDS, 173, 174
Alcohol gel, 723
Alefacept, 31, 36, 195, 200, 201
Alemtuzumab, 639
Alginate, 745, 746
Alkaloids, 672
Alkylation therapies, 638
Allelic heterogeneity, 41, 43
Allergic contact dermatitis, 275–282
granuloma, 277
Allergic contact hypersensitivity, 17
Allergy
allergy card, 310
allergy diagnostics, 306, 309, 310
anaphylaxis, 298–300
benzodiazepam allergy, 312
contact dermatitis (ACD), 301, 310
food allergy, 298
skin, 179
vasculitis, 427
venom allergy, 298
Allogenic fibroblasts, 557
Alloknnesia, 123
Allopurinol, 321–324, 460
All-trans retinoid acid
4-hydroxy all-trans retinoid acid, 77
4-oxo all-trans retinoid acid, 77
Allopecia areata, 48, 499–505
Alpha-melanocyte stimulating hormone, 19
Ambrosia artemisifolia, 281
5-Aminolevulinic acid (5-ALA), 94, 95
Atorvastatin, 242
Amorolfin, 513
Amoxicillin–clavulanic acid, 134
Amoxicillin, 304–306
Amyloidosis, 487–489
5-amino levulinic acid, 105
Anal carcinoma, 174
Anaphylaxis, 724, 726
Anchoring fibrils, 551, 554, 557
Androgen, 360, 361, 363, 367
  hormone receptors, 360
  receptor blockers, 363
Androgenetic alopecia, 499–505
Anemia, 459, 638
Angioedema, 247–249, 253–257, 259, 260, 297–300
Angiosarcoma
  angiosarcoma of the elderly, 666
  post irradiation angiosarcoma, 666
Angiotensin (AT)
  angiotensin-converting enzyme (ACE) antagonists, 299
  angiotensin-converting enzyme(ACE)-inhibitors, 299, 300, 305
  angiotensin-receptor antagonists, 299, 300
Animal models, 313
Anterior uveitis, 459
Arthralgia, 729
Antiandrogen, 363, 367, 369
Anti-anthrax serum, 138
Antibiotics, 745
Antibody deficiency disorder, 579–580
Anti-CD-52 antibody, 436
Anti-CD-20 antibody rituximab, 300
Anticonvulsants, 241
Anticonvulsives, 310, 312, 313
Antidepressants, 242
Antigen, 248, 250, 254–257, 259
  presentation, 16–19
  presenting cells, 16–17, 19
Anti-histamine(s), 228, 247, 256, 257, 260–261, 324
Anti-inflammatory biological, 230
Antimalarials, 460–462, 464, 465
Antimicrobial
  agents, 745
  peptides, 5, 226
  therapy, 131
Antioxidants, 731
Antioxidant therapies, 445–446
Antisense strategy, 557
Antithymocyte globulin (ATG), 436–438
Anti-TNF-α
  agents, 193, 195, 201
  drugs, 460
  therapy, 744
Antiviral therapy, 158
Apligraf®, 746, 747
Apoptosis, 87–90
Appendageal penetration, 59
Apricitabine, 176
APUD system, 670
Area under the curve (AUC), 21, 24, 26
Aromatic anticonvulsants, 322–323
Aromatic hydrocarbons, 726, 731, 732
Arsenic, 732
Arterial medial hypertrophy, 728
Arterial ulceration, 738
Arteriovenous malformations (AVMs), 644, 646–647, 650, 651, 654–655
Arthritis, 459, 464, 465
Aspirin, 381, 462, 743
Asthma, 724
Ataxia-telangiectasia (AT), 578–579
Atopic dermatitis (AD), 48, 87–90, 123, 225–231, 326–327, 677–679, 693–695, 701, 702
Atopic eczema, 228
Atrophy, 551, 553, 554
Atypical fibroxanthoma, 669–670
Atypical post irradiation vascular lesions, 668
Autoallergens, 227
Autoantibody, 228, 247, 249, 253, 255, 257, 259, 260
Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome, 575
Autoimmune thyroiditis, 300
Auto-inflammation, 694
Autologous bone-marrow derived cells, 749
Autologous melanocytes, 449
Autosomal dominant inheritance, 44
Autosomal recessive inheritance, 44–45
Avexa, 176
Avocado, 725
Avoidance of UV-light exposure, 479, 480
Azathioprine, 228, 430
Azelaic acid, 363–366, 379, 381, 382
Azithromycin, 366, 379

B
Bacillus anthracis, 137
Bacterial resistance, 365, 366, 368
Balneophototherapy, 199
Banana, 725
Barrier creams, 722
Barrier function, 57–61
Bartonella henselae, 142–143
Bartonella infections, 142–144
Basal cell carcinoma (BCC)
  clinical variants, 603
curettage and electrodesiccation, 605
Gli proteins, 600
Gremlin-1, 601
Mohs micrographic surgery, 606
morphoeaform, 601–604
PTCH allele, 600
p53 tumor suppressor gene, 601
sun-exposed dorsal hands, 602
topical photodynamic therapy, 607, 608
treatment guidelines, 605
Basement membrane zone, 3, 7
B cell-directed therapy, 411
Becaplermin, 746
Behcet’s disease, 427, 428, 431
Bellinostat, 639
Benefit-to-risk ratio, 694
Benzoyl peroxide, 363–366, 369, 379, 382
Benzyl benzoate, 696
Betamethasone
dipropionate, 446
valerate, 446
Bexarotene, 82, 637
Bioavailability, 21, 22, 24
Biologic response modifiers, 510, 511
Biologics, 217, 219–220
Biomaterial science, 749
Biosurgery, 745
Biphenyls, 726
Index

Bleaching agents, 450–453
Bleaching treatments, 79
Blepharitis, 376, 378
Bone marrow suppression, 638
Botox, 709, 710, 713
Botulinum toxin type A (BTX-A), 520–521
Bowen’s disease, 106, 107, 109, 610
Buerger disease, 738
Bullous congenital ichthyosiform erythroderma, 83
Bullous exfoliation, 434
Bullous impetigo, 130
Burns, 717–720

C
Cadherin, 7–9
Calcineurin inhibitors, 229, 240
Calciosis cutis, 491–493
Calcipotriol, 511
Calciproteine, 448
Calcitonin gene-related peptide (CGPR), 243
Calcium antagonists, 743
Calcium channel blockers, 730
Calyptomabacterium granulomatis, 169
Camouflage, 452, 453
Camphor, 236
Candidiasis, 151–152
Capillary-leak syndrome, 639
Capsaicin, 239, 242
Carbapenem derivatives, 307
Carbon dioxide (CO2) lasers, 95–96, 460, 462, 464, 712, 713
Cardiolipin, 165
β-Carotene, 479, 481
Cartilage-hair hypoplasia syndrome (CHHS), 576
Cataract, 445
Cathelicidin, 226
Cat-scratch disease, 143
Cavernous hemangioma, 645
Cell-based treatments, 746–747
Cell-cell interactions, 735
Cell-matrix interactions, 735
Cells
  cell-matrix adhesion, 7, 9
  Langerhans cells, 5, 9
  mast cells, 5, 6
  Merkel cells, 5
  progenitor cells, 4, 5
  T-cells, 5, 9
Cellulitis, 132–133
Cephalaxin, 130
Cephalexin, 306, 307
Cetuximab, 615
Chancroid, 169
Chediak-Higashi syndrome (CHS), 586
Chemical leukoderma, 731
Chemokines, 17, 18, 226, 227
Chemotherapy
  adjuvant chemotherapy, 672
  palliative chemotherapy, 672–673
Chestnut, 725
Chickenpox, 693
Chloracne, 726–728
Chlorambacil, 460, 462, 464
Chlorambucil doxorubicine, 638
Chlorhexidine, 745
Chlormadinone, 363
Chloroquine, 479–481
Cholestatic hepatopathy, 434
Chondrosarcomas, 669, 671
Chronic actinic dermatitis (CAD), 285, 286, 292–294
Chronic graft-versus-host-disease (cGVHD), 434–439
  extensive form of cGVHD, 435
  grading of cGVHD, 435
  limited form of, 435, 437, 439
Chronic granulomatous disease (CGD), 583–584
Chronic hepatitis, 740
Chronic lymphocytic leukaemia, 463
Chronic mucocutaneous candidiasis (CMC), 575–576
Chronic superficial dermatitis, 207
Churg-Strauss-Syndrome, 427, 428
Ciclopiroxolamine, 513
Ciclosporin, 193, 195, 196, 199, 200
Cilostazol, 743
Ciprofloxacin, 137
Cisplatin, 672
Claciphylaxis, 741, 743
Claritomycin, 379, 382
Clearance process, 24–25
Clear cell sarcoma (malignant melanoma of soft parts), 670
Clindamycin, 130, 131, 365, 366, 379, 389
Clinical pharmacology, 21
Clobetasol propionate, 446, 448
Clofazimine, 462
Clomipramine, 242
Clonal dermatitis, 207
Clonidin, 379, 381, 384
Clopidrogel, 743
Coal, 731, 732
Coal tar products, 209
Cockayne syndrome (CS), 591–592
COL7AI, 554
COL17AI, 553
Colchicine, 429
Cold, 236, 239–240
Colitis, 322
Collagen-glycosaminoglycan matrix, 747
Collagen XVIII, 6
Colloidal oatmeal, 722
Combination chemotherapy, 638
Comedones, 359–364, 367, 369
Complement disorders, 581–582
Compression bandage, 743
Condylomata acuminata, 699–700
Congenital nevi, 115
Conjunctival injection, 697
Conjunctival telangiectasias, 378
Conjunctivitis, 376, 378
Connective tissue, 5–7, 9
Connective tissue diseases, 736, 744
Contact allergens, 276
Contact allergy, 275–277, 279, 281, 282
Contact dermatitis, protein contact, 724–726
Contact urticaria, 718, 724–727
Contrast agents, 299, 307, 309
<table>
<thead>
<tr>
<th>Term</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copenhagen allergy study</td>
<td>281</td>
</tr>
<tr>
<td>Corneocyte</td>
<td>58, 59</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td></td>
</tr>
<tr>
<td>intralesional corticosteroids</td>
<td>460</td>
</tr>
<tr>
<td>potent corticosteroids</td>
<td>462</td>
</tr>
<tr>
<td>systemic corticosteroids</td>
<td>460, 462</td>
</tr>
<tr>
<td>Corticosteroid therapy</td>
<td>324, 325</td>
</tr>
<tr>
<td>Corticotrophin releasing hormone</td>
<td>369</td>
</tr>
<tr>
<td>Cosmetic surgery</td>
<td></td>
</tr>
<tr>
<td>clinical characteristics and diagnosis</td>
<td>540</td>
</tr>
<tr>
<td>cryotherapy</td>
<td>541</td>
</tr>
<tr>
<td>etiology and pathophysiology</td>
<td>539</td>
</tr>
<tr>
<td>facial resurfacing</td>
<td>542–543</td>
</tr>
<tr>
<td>KTP laser</td>
<td>541</td>
</tr>
<tr>
<td>leg vein treatment</td>
<td>543</td>
</tr>
<tr>
<td>light electrodessication</td>
<td>541</td>
</tr>
<tr>
<td>lip blepharoplasty</td>
<td>543</td>
</tr>
<tr>
<td>Q-switched lasers and scissor excision</td>
<td>541</td>
</tr>
<tr>
<td>soft-tissue augmentation materials</td>
<td>542</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>740</td>
</tr>
<tr>
<td>Cryosurgery</td>
<td>382</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>461, 462</td>
</tr>
<tr>
<td>CTLA4</td>
<td>34–35</td>
</tr>
<tr>
<td>Cucumis melo superoxide dismutase</td>
<td>448</td>
</tr>
<tr>
<td>Cutaneous anthrax</td>
<td>137–138</td>
</tr>
<tr>
<td>Cutaneous leishmaniasis</td>
<td>186</td>
</tr>
<tr>
<td>Cutaneous lymphomas</td>
<td>633–640</td>
</tr>
<tr>
<td>cutaneous B-cell lymphomas (CBCL)</td>
<td>634, 640</td>
</tr>
<tr>
<td>cutaneous T-cell lymphomas</td>
<td>633–640</td>
</tr>
<tr>
<td>Cutaneous T-cell lymphoma</td>
<td>82</td>
</tr>
<tr>
<td>Cutaneous tuberculosis</td>
<td>140–142</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>464, 638, 672</td>
</tr>
<tr>
<td>Cyclosporin A</td>
<td>436</td>
</tr>
<tr>
<td>Cyclosporin A</td>
<td>462</td>
</tr>
<tr>
<td>Cyproterone</td>
<td>363, 367</td>
</tr>
<tr>
<td>Cytochrome P-450 (CYP)</td>
<td>21, 24–26, 63, 68–69, 73, 78, 179, 322, 323</td>
</tr>
<tr>
<td>Cytochrome P450-isoenzymes</td>
<td>312</td>
</tr>
<tr>
<td>Cytokine-targeting agents</td>
<td>411</td>
</tr>
<tr>
<td>Cytotoxic T lymphocyte antigen-4 (CTLA4)</td>
<td>34–35</td>
</tr>
<tr>
<td>Cytokines</td>
<td>15–19</td>
</tr>
<tr>
<td>D</td>
<td>672</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>672</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>437, 438</td>
</tr>
<tr>
<td>Dactinomycin, 672</td>
<td></td>
</tr>
<tr>
<td>Dapsone</td>
<td>321, 323, 367, 379, 382, 429, 462, 465, 744</td>
</tr>
<tr>
<td>Darier’s disease</td>
<td>46, 78, 567–568</td>
</tr>
<tr>
<td>Darier’s sign</td>
<td>265, 266</td>
</tr>
<tr>
<td>Debridement</td>
<td></td>
</tr>
<tr>
<td>autolytic debridement</td>
<td>745</td>
</tr>
<tr>
<td>surgical debridement</td>
<td>745, 746</td>
</tr>
<tr>
<td>Decreasing</td>
<td>382</td>
</tr>
<tr>
<td>Defensin 1, 2 and 3</td>
<td>226</td>
</tr>
<tr>
<td>Defensins</td>
<td>5</td>
</tr>
<tr>
<td>Deficiency of protoporphyrinogen oxidase</td>
<td>471</td>
</tr>
<tr>
<td>Delayed-type hypersensitivity</td>
<td>301–305</td>
</tr>
<tr>
<td>Demodex folliculorum</td>
<td>375, 382</td>
</tr>
<tr>
<td>Demyelinating neuropathy</td>
<td>728</td>
</tr>
<tr>
<td>Dendritic cells (DC)</td>
<td>227</td>
</tr>
<tr>
<td>Denileukin Diftitox</td>
<td>638</td>
</tr>
<tr>
<td>Dental care</td>
<td>556</td>
</tr>
<tr>
<td>Dentist</td>
<td>724, 728, 732</td>
</tr>
<tr>
<td>Depression</td>
<td>179</td>
</tr>
<tr>
<td>Dermabrasion</td>
<td>382, 712, 713</td>
</tr>
<tr>
<td>Dermagraft®</td>
<td>747</td>
</tr>
<tr>
<td>Dermal–epidermal junction (DEJ)</td>
<td>549–551, 557</td>
</tr>
<tr>
<td>Dermal mast cells</td>
<td>236, 239</td>
</tr>
<tr>
<td>Dermatofibrosarcoma (protuberans)</td>
<td></td>
</tr>
<tr>
<td>classic dermatofibrosarcoma</td>
<td>661</td>
</tr>
<tr>
<td>myxofibrosarcoma</td>
<td>661</td>
</tr>
<tr>
<td>Dermatologic surgery</td>
<td></td>
</tr>
<tr>
<td>children</td>
<td>118</td>
</tr>
<tr>
<td>clinical characteristics and diagnosis</td>
<td>114–115</td>
</tr>
<tr>
<td>congenital nevi and precancerous lesions</td>
<td>115</td>
</tr>
<tr>
<td>elliptical excision</td>
<td>116–117</td>
</tr>
<tr>
<td>etiology and pathogenesis</td>
<td>113–114</td>
</tr>
<tr>
<td>experimental approach and global variations</td>
<td>118</td>
</tr>
<tr>
<td>Mohs surgery</td>
<td>117</td>
</tr>
<tr>
<td>reconstructive surgery</td>
<td>117–118</td>
</tr>
<tr>
<td>skin biopsy</td>
<td>115–116</td>
</tr>
<tr>
<td>Dermoscopy</td>
<td>623–624</td>
</tr>
<tr>
<td>Desensitization</td>
<td>311, 314</td>
</tr>
<tr>
<td>Desmoglein</td>
<td>389, 390, 400</td>
</tr>
<tr>
<td>Desmedos</td>
<td>661</td>
</tr>
<tr>
<td>Desmosomes</td>
<td>8, 9, 11, 551, 554</td>
</tr>
<tr>
<td>Desquamation</td>
<td>445</td>
</tr>
<tr>
<td>Detergent hand wash</td>
<td>722</td>
</tr>
<tr>
<td>Developmental endothelial locus-1 (Del-1) protein</td>
<td>645</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>insipidus</td>
<td>459</td>
</tr>
<tr>
<td>mellitus</td>
<td>738–740, 742, 743</td>
</tr>
<tr>
<td>Diabetic foot ulcer</td>
<td>739, 746, 747</td>
</tr>
<tr>
<td>Dibenzoynes</td>
<td>726, 727</td>
</tr>
<tr>
<td>Dicloxacillin, 130</td>
<td></td>
</tr>
<tr>
<td>Didanosine</td>
<td>176</td>
</tr>
<tr>
<td>Differentiation program</td>
<td>4</td>
</tr>
<tr>
<td>Digital dermatosis</td>
<td>207</td>
</tr>
<tr>
<td>Dioxins (polychlorinated dibenzodioxines)</td>
<td>726</td>
</tr>
<tr>
<td>Diphtheria toxin (DT)</td>
<td>639</td>
</tr>
<tr>
<td>Discoid lupus erythematosus</td>
<td>78</td>
</tr>
<tr>
<td>Disinfectants</td>
<td>555</td>
</tr>
<tr>
<td>Dissecting cellulitis of the scalp</td>
<td>369</td>
</tr>
<tr>
<td>Distal and lateral subungual onychomycosis (DLSO)</td>
<td>512</td>
</tr>
<tr>
<td>Dizziness</td>
<td>177, 179</td>
</tr>
<tr>
<td>DNA repair disorder</td>
<td></td>
</tr>
<tr>
<td>Cockayne syndrome (CS)</td>
<td>591–592</td>
</tr>
<tr>
<td>nucleotide excision repair (NER) system</td>
<td>589, 590</td>
</tr>
<tr>
<td>trichothiodystrophy (TTD)</td>
<td>591–592</td>
</tr>
<tr>
<td>xeroderma pigmentosum (XP)</td>
<td>590–592</td>
</tr>
<tr>
<td>Doxepin</td>
<td>242</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>672, 673</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>137, 366, 368, 460</td>
</tr>
<tr>
<td>Doxycycline hyclate</td>
<td>382</td>
</tr>
<tr>
<td>Drosophila patched gene (PCH)</td>
<td>600</td>
</tr>
<tr>
<td>Drospirenone</td>
<td>363, 367</td>
</tr>
<tr>
<td>Drug–drug interactions</td>
<td>21, 25, 26, 78</td>
</tr>
<tr>
<td>Drug-induced</td>
<td></td>
</tr>
<tr>
<td>autoimmune reactions</td>
<td>300</td>
</tr>
<tr>
<td>hypersensitivity syndrome</td>
<td>303–304</td>
</tr>
<tr>
<td>photosensitivity</td>
<td>285, 286, 294–295</td>
</tr>
</tbody>
</table>
Drug monitoring, 176, 178–179
Drug reaction
  bullous allergic drug reaction, 301–305
  erythema multiforme-like drug reaction, 302
  fixed drug reaction, 301
Drug tolerance, 21
Drug toxicity, 21
Drug transporters, 21, 25–26
Dystrophic epidermolysis bullosa, 41
  dominant dystrophic EB, 554
  Hallopeau-Siemens recessive dystrophic EB, 554
  non-Hallopeau-Siemens recessive dystrophic EB, 554

E
EBV associated lymphoproliferative disease, 436
Ectoparasitic infestations
  pediculosis, 181–183
  scabies, 183–184
Eczeoma herpeticum, 226, 227, 230
Eczeoma molluscum, 230
Ecematous lesion, 678
Edema factor, 137
Efalizumab, 31, 36
Eicosanoids, 18
Elastin, 6
Electrosurgery, 381, 382
Elephantiasis genitooanalericis ulceroasa, 168
Elicitation, 275, 276, 280, 281
Elliptical excision, 114, 116–118
Elvucitine, 176
Embolism, 738
EMLA, 703
Emollients, 228–230
Endostatin, 6
Endothelial cells, 6–8, 11
Endothelin-1, 728
Entamoeba histolytica, 184, 185
Environmental factors, 226, 231
Enzyme-linked immunosorbent assay (ELISA), 390, 393, 394, 400, 401
Enzyme replacement therapy, 483
Eosinophil, 325–331
Eotaxin, 325–327, 329, 331
Epidermal barrier, 226
Epidermal growth factor receptor, 673
Epidermal stem cells, 557
Epidermolysis bullosa ichthyosis, 695, 702
Epidermiditis, 167, 168
Epithelial-to-mesenchymal transition (EMT), 5
Epithelioid sarcoma, 670
Epoxido hydrolases, 312
Erbium:YAG laser, 96–97
Eruptions, 277
  lichenoid eruptions, 277
  lymphomatoid eruptions, 277
  scleroderma-like eruptions, 277
Erysipelas, 132
Erythema elevatum diutinum (EED), 342–343
Erythema multiforme, 277
Erythema nodosum (EN), 460
Erythroderma, 434, 435
Erythroderma, 637–638
Erythromycin, 130, 365–368, 555
Esophageal strictures, 556
Esophagus dilatation, 556
Estrogen, 363
Etanercept, 32–34, 36, 195, 201, 437, 438, 460, 464
Etoposide, 464, 701
Etravirin, 176, 177
Etretinate, 78, 80–81, 83
European Organization for Research and Treatment of Cancer (EORTC), 633, 634
Evitegravir, 176
Excimer
  308 nm excimer laser, 447
  308 nm monochromatic excimer light, 447
Excimer laser, 210
Excimer light, 88–89
Extracellular matrix (ECM), 3, 5–7, 11
Extracorporeal chemotherapy (ECP, extracorporeal photophoresis), 437
Extracorporeal photophoresis (ECP), 635, 637–638

F
Fabry disease, 490–491
Facial atrophy, 540
Facial skin sagging, 540
Fatigue, 637, 638, 640
FEC! gene mutation, 470
Fever, 638–640
Fiber supplements, 556
Fibrillin, 8
Fibrotic nodules, 730
Filaggrin, 11
Finasteride, 503, 505
Fire extinguishers, 719
Flash lamp pumped pulsed dye laser, 644, 651–652
Fluconazole, 513, 514
Fluorescence treponema antibody absorption test (FTA-abs), 166
Flushing, 376, 379–381
Flutamide, 367
Fluoxetamine, 237
Foam dressings, 745, 746
Focal adhesions, 9, 10
Follicular
  epidermal hyperproliferation, 360, 364
  occlusion triad, 369
Foliculitis, furuncles, and carbuncles
  bacteremia, 131
  clinical characteristics and diagnosis, 131
  etiology and pathophysiology, 130–131
  experimental approaches, 131
  moist heat, drainage, 131
Fosalvudine, 176
Fozivudine, 176
Fractional photothermolysis, 102
Francisella tularenis, 144, 145
Freckles, 445
Fucidic acid, 555
Fumarates, 465
Fumaric acid ester, 200
Fumaric esters, 462
Gabapentin, 124, 125, 241, 243
Gastrointestinal signs, 724
Gastrostomy button insertion, 556
Gemcitabine, 672, 673
Gene-environment interactions, 226
General anesthesia, 309
Gene therapy, 479, 483–484
-- delivery systems, 49
revertant mosaicism, 50–51
Genetic counseling, 556
Genetic/locus heterogeneity, 41–43
Genetics
autosomal dominant inheritance, 44
autosomal recessive inheritance, 44–45
basics, 39
chromosomal abnormalities, 47–48
de novo mutations and germline mosaicism,
46–47
genetic disease, 40–41
incomplete penetrance and delayed onset disease, 46
Mendelian genetics, 41–43
polygenic diseases, 48
principles, 39
variable expression, 46
X-linked dominant inheritance, 45
X-linked recessive inheritance, 45–46
Germline mosaicism, 46–47
Ginko Biloba, 449
Gli proteins, 600
Glomuvenous malformation (GVM), 645, 649, 653
Gloves, 721–726, 729
Glucocorticoids, 299, 310, 311
Glucose-6-phosphate dehydrogenase (G6PD), 70
Glutathione S-transferase-based (GST) resistance, 182
Glycerine, 722
Glycerol
glycerol monothioglycolate, 724
GM-CSF, 18
Gonorrhea
Neisseria (N.) gonorrhoeae, 165, 167
Grafting, 462
full-thickness punch grafting (“minigrafting”), 449
split-thickness grafting, 449
suction blister grafting, 449
Grafts
-- cellular graft, 449–451
-- composite grafts, 747
cultured grafts, 747
epidermal grafts, 747
-- punch biopsy grafts, 746
split-thickness skin grafts, 746
tissue graft, 449, 451
Graft-versus-host disease, 216, 240
Granulocyte colony stimulating factor (G-CSF), 18
Granulocyte-macrophage, 463
Granuloma
actinic granuloma, 461, 462
elastolytic granuloma, 464
foreign body granuloma, 460, 464, 465
generalized granuloma, 461, 462
granuloma annulare, 461–462
localized granuloma, 461
noncaseating granuloma, 460
palisaded granuloma, 462
perforating granuloma, 461
sarcoid granuloma, 460, 462, 464, 465
subcutaneous granuloma, 464
Granuloma inguinale (Donovanosis), 169–170
Granulomatous rosacea, 464–465
Griscelli syndrome (GS), 586
Growth factor
growth factor therapy, 746
Platelet Derived Growth Factor-BB (rhPDGF-BB), 746
recombinant human growth factor, 746
GSK 364735, 176
Guideline, 251–255, 258, 260, 261
Haemophilus ducrey, 169
Hair dyes, 731
Half-life, 22, 24, 26
Hand dermatitis, 240
Hand dermatitis, 240
H1-antihistamines, 240
Hapten, 17, 18
Haptenization, 17
Hashimoto-Pritzker variant, 701
Hay-Wells syndrome, 41
H2-blockers, 240
Heat shock protein HSP70, 313, 314
Heerfordt syndrome, 459
Heliothepulbry pylori, 375
Helium-neon laser irradiation, 452
Hemangiomas, 693, 698–699
Hemangiomias, 693, 698–699
Hematin, 480, 481
Heme arginate, 480, 481
Hemidesmosomes, 7, 9
Hemin, 480, 482
Hemochromatosis, 493–494
Hereditary angioneurotic edema (HANE), 300
Herpes gestationis (HG), 682–685
Herpes simplex virus (HSV), 157–158
Herpes zoster, 159
Hidradenitis suppurativa, 369
High-affinity IgE receptor, 17
High-caloric and protein-fortified foods, 556
High-dose intravenous immunoglobulins, 430
Highly active antiretroviral therapy (HAART), 176
Hirsutism, 361, 367
Histamine, 121–125
Histamine receptors, 236
Histiocytosis
hemophagocytic lymphohistiocytosis, 701
Langerhans cell (LC) histiocytosis, 700–702
malignant histiocytosis, 701
non-Langerhans cell histiocytosis, 701
Histone deacetylase inhibitors, 639–640
Hodgkin (lymphomas), 463, 465
Hodgkin’s disease, 236
Human herpesvirus 6 (HHV-6), 322–324
Human immunodeficiency virus (HIV), 173–176,
178, 179, 331
Human papillomavirus (HPV), 160
Humectants, 722
Hyaluronic acid, 709, 711
Hydrocolloids, 722, 746
Hydrogels, 745
Hydroxychloroquine, 460, 462, 465
Hydroxyurea, 200, 741
Hygiene hypothesis, 226, 231
Hyperbaric oxygen, 462
Hyperbilirubinaemia, 177
Hypercalcemia, 459, 460
Hypercholesterolaemia, 82
Hyperhidrosis
apocrine sweat glands, 517
axillary treatment algorithm, 522
botulinum toxin type A (BTX-A), 520–521
eccrine glands, 517, 521
etiology, 518–519
histopathology, 517–518
iontophoresis, 520
palmoplantar treatment algorithm, 522
pathophysiology, 518
primary hyperhidrosis, 519
secondary hyperhidrosis, 518, 519
sympathectomy, 521
systemic therapy, 519–520
topical therapy, 519
Hyperimmune serum therapy, 138
Hyperimmunoglobulinemia E Syndrome (HIES), 585
Hyperlipidaemia, 177–179, 738, 742
Hyperlipidemia/hypercholesterolemia, 637
Hyperlipidemia/hypercholesterolemia
Hyperpersensitivity syndrome, 177, 179, 321–325
Hypertension, 737, 738, 743
Hypertrichosis universalis congenita, 48
Hypertriglyceridaemia, 82
Hypohidrotic ectodermal dysplasia with immunodeficiency
(HED-ID), 577–578
Hypopigmentation, 79, 99, 101, 102, 694
Hypothyroidism, 82, 637
Hypoxia-regulated cytokines, 746
I
Ichthyosis, 561–567
lamellar ichthyosis, 83
X-linked recessive ichthyosis, 83
Icilin, 239–240
Idiosyncratic reactions, 22
Ifofamide, 672, 673
IgE, 248, 250, 253–257, 259, 260
IgE-sensitization, 225
Illoprost, 743
Iloprost, 730
Imatinib (Glivec®), 659, 661
Imipenem, 307
Imiquimod, 700
Immune mechanisms
adaptive immune mechanisms, 226
innate immune mechanisms, 226
Immune suppression, 87–88
Immunodeficiency, 465
Immunodiffusion assays, 136
Immunomodulatory agents, 160
Immunosuppressants, 351, 352
Immunosuppressive agents, 410–411, 419, 423, 429, 430
Immunotherapy, 725
Impetigo and ecthyma, 129–130
Indinavir, 176, 179
Infantile hemangioma (IH), 693, 698, 699
Infliximab, 32, 33, 195, 201, 462, 464
Inhibition
ectopeptidase inhibition, 369
leukotriene inhibition, 369
Immune suppression, 15, 19
Integrase inhibitor, 173, 176
Integrin, 7, 9
Interferon
IFN-α, 464, 635, 637, 699
IFN-γ, 18, 459, 462
Interleukin (IL)
adaptive IL, 16
IL-2, 639
IL-5, 327, 329–331
IL-6, 17, 18
IL-7, 18
IL-10, 18
IL-12, 17, 18
IL-12/23 p40, 35
IL-15, 18
IL-18, 18
IL-19, 18
IL-20, 18
IL-31, 241, 243
IL-1β, 17
Interpalpebral conjunctival hyperemia, 378
Intrahepatic cholestasis of pregnancy (ICP), 679–682
Intralesional administration, 640
Intralesional steroids, 446
Intralesional triamcinolone, 460
Intravenous antibiotics, 133
Intravenous corticosteroid, 697
Intravenous immunoglobulin (IVIG), 35, 36, 135, 311, 394, 395, 397, 398, 411, 419, 423, 578, 580, 581, 585, 586, 592, 697
In vitro test, 309, 310, 314
Iontophoresis, 520
Irritant contact dermatitis, 277, 279, 281, 282, 720–723
Ischemia, 736, 743
Isotretinoin, 637
Itch, 121–125
Itraconazole, 150–155, 513, 514
Ivermectin, 183, 696
J
Jarisch-Herxheimer-reaction, 300
Joint contractures, 730
Junctions
adherens junctions, 7–9
gap junctions, 7, 9
tight junctions, 8–10
Juvenile xanthogranuloma, 701
Kaposi’s sarcoma, 80, 173, 174, 176
Kawasaki disease, 696–698
Keratinocytes, 4, 5, 7–9, 11, 275
Keratins, 4, 10, 11
Khellin, 446
Kit (CD117), 264
Kiwi, 725

L
Laminin, 7
Lamivudine, 176
Langerhans cells, 16, 19, 275, 276
Langerin, 16
Lanolin, 722
Laser
   carbon dioxide laser, 700
   pulsed dye laser, 700
Lecithin:retinol acyltransferase (LRAT), 77
Leflunomide, 460
Leiomyosarcoma, 663–664, 672
Leishmania amazonensis, 187
Leishmania major organisms, 187
Lentigines, 445, 540
Lentiviral, 483
Leprosy
   chronic granulomatous disease, 138
   multidrug therapy, 139, 140
   tuberculoid and lepromatous form, 139
   Ziehl-Neelsen staining, 139
Leukocyte adhesion deficiency (LAD), 584
Leukodermapunctata, 445
Leukemia, 459
Leukotrienes, 19
Malignancies, 461, 463, 464, 740, 741
Malignant melanoma, 621–630
   classification and diagnosis, 622–625
   early detection, 623
   surgical treatment, 626
   therapy, 627–629
Malignant peripheral sheath tumor, 668
Malignant schwannoma, 668
Malnutrition, 736
Methotrexate (MTX), 196, 199–201, 210, 228, 430, 436, 638, 672
Methyldibromoglutaronitrile, 281
Methyl ethyl aminolevulinic acid, 95
Metastatic Crohn's disease, 464
Metastatic tuberculosis abscess (MTA), 141
Methotrexate (MTX), 196, 199–201, 210, 228, 430, 436, 638, 672
Methyldibromoglutaronitrile, 281
Methyl ethyl aminolevulinic acid, 95
Metronidazole, 378, 379, 381, 382, 384
Microcirculation, 6
Micropigmentation, 452
Miescher’s disciform granulomatosis, 462
Minocycline, 321–323, 366, 368, 460, 465
Minoxidil, 501, 503–504
Moisturizers, 722
Index

Molluscum contagiosum (MC), 160–161
Monilethrix, 46
Monobenzylether of hydroquinone (MBEH), 450, 452
Montelukast, 241
Morchova, Motretinide, 79
MRSA, 131
Mucha-Habermann disease, 208
Mulliken classification, 643, 644
Multibacillary leprosy, 139, 140
Multidrug resistance-associated proteins (MRPs), 81
Multiple myeloma, 464
Mupirocin ointment, 130
Muscle relaxants, 299, 306, 309–311
Myalgia, 638
Mycobacterium leprae, 138–140
Mycobacterium tuberculosis, 140, 142, 459
Mycophenolate mofetil (MMF), 30–31, 36, 228, 230, 430, 437, 438, 463
Mycosis fungoides, 207, 208, 633–635
Myofibroblasts, 6

N
N-acetylcysteine, 311
N-Acetyltransferase (NAT), 69
Nadolol, 381
Nail psoriasis
  acitretin therapy, 511
  biologic response modifiers, 510, 511
  clinical characteristics and diagnosis, 509–510
  intralesional steroid injection, 510–511
  systemic therapy, 510, 511
  topical therapy, 510–511
Nalmefene, 242
Naloxon, 379, 381
Naloxone, 242
Naltrexone, 242, 243
Narrow band ultraviolet B phototherapy, 87–90, 196, 198–199, 201, 228, 229, 447, 448, 636
Necrobiosis lipoidica, 739
Necrotic tissue, 134
Necrotizing fasciitis, 134–135
Negative pressure wound therapy (NPWT), 748
Nephrolithiasis, 177, 179
Nerve growth factor (NGF), 242
Netherton syndrome, 563, 565–566
Neurigenic sarcomas, 668
Neuroendocrine (Merkel cell, trabecular) carcinoma, 670
Neurofibromatosis, 668, 669
Neurofibrosarcoma, 668, 672
Neurohormones, 18
Neuronal sensitization, 1123–125
Neuropathic itch, 124
Neuropathic ulcer, 740
Neuropathy, 738, 739
Neuropetin, 143
Neurophilic eccrine hidradenitis (NEH), 345–347
Nevirapine, 176
Nevus of Ota, 532–533
New World leishmaniasis, 186
Niacinamide, 463
Nitrogen mustard, 636
Non-atopic eczema, 225, 226
Nonmelanoma skin cancer (NMSC)
  basal cell carcinoma (BCC), 600–608
  squamous cell carcinoma (SCC), 608–615
Non-nucleoside reverse transcriptase inhibitors (NNRTIs), 173, 176, 179
Nonsteroidal anti-inflammatory drugs (NSAIDs), 297, 299, 305, 306, 310
Notalgia parasthetica, 239, 241
Nucleic acid amplification tests (NAATs), 167, 168
Nucleoside reverse transcriptase inhibitors, 176, 179
Nucleotide excision repair (NER) system, 589–591
Nylurea drugs, 305

O
Obesity, 736, 737
Occlusion, 59–60
Occupational dermatose, 717–733
Occupationally induced skin cancer, 732
Occupational physician, 717, 718, 721
Octenidin, 745
Ofuji disease, 328–330
Oil
  distillates, 732
  or tar acne, 728
Old World disease, 186
Omalizumab, 230, 311
Onco-retroviral, 483
Ondanestron, 381
Ontak, 638
Oxypentifylline, 730
Paclitaxel, 673
Palmoplantar keratoderma, 568–572
Panobinostat, 639
Pan tyrosin kinase inhibitors, 673
Pap smear, 160
Parapsoriasis, 208–210
Paronychia, 179
Paroxetine, 242
Patch, 207, 208
Parapsoriasis, 208–210
Paroxetine, 242
Patch/plaque disease, 635–637
Pathogen associated molecular pattern (PAMP), 226
Pattern recognition receptors (PRR), 226
Paucibacillary leprosy, 139
Pediculosis etiology and pathophysiology, 181
knockdown resistance, 181
permethrin resistance, 182
pyrethroids, 181
Pemphigoid, 390–393, 399
Pemphigus, 389–394, 396–402
Penicillin benzathine penicillin, 166, 167
Penicillin G, 306
Penicillin V, 306
Penicillin V, 306
Pentoxifylline, 429, 460, 462, 463, 743
Percutaneous absorption, 23
Percutaneous sclerotherapy, 653, 654
Perfluoralkylpolyether, 722
Perianal condylomas, 694, 699
Perineurial sarcomas, 669
Perioral dermatitis, 379, 381, 383
Permethrin, 382, 696
Permethrin resistance, 182
Persistent edema in rosacea (Morbihan’ disease), 383–384
Pethidine, 480, 481
Pharmacodynamics, 22
Pharmacogenetics, 22, 26, 27
Pharmacogenomics, 22, 26
Pharmacokinetics absorption, 22
distribution, 23
excretion, 25
metabolism, 24
Pharyngitis, 697
Phenols, 719
Phlebotomy, 479, 481
Phosphodiesterase inhibitor, 743
Photocopying, 79, 80
Phototesting, drug, 287–288, 295
Phototherapies, 369, 635, 636
Photo(chemo)therapy, 210
Phototoxic reactions, 286, 288, 294, 295
Pigmentary disorders, 730–732
Plasmapheresis, 311
Platelet aggregation, 730
Poikiloderma, 435
Poikiloderma atrophicans vasculare, 207, 208
Polyethylene glycol, 719
Polyhexanid, 745
Precancerous lesions, 115
Precocious puberty, 369
Prednisone, 698, 701
Pregabalin, 241
Pressure ulcers (decubitus), 739
plasma skin resurfacing technology, 97
Q-switched and long-pulsed laser systems, 99
yellow and green light lasers, 99–100
Photodynamic therapy, 106–110, 384
Photodynamic treatment, 369, 370
Photopatch testing, 287–288, 294
Phototesting, drug, 287–288, 295
Phototherapies, 369, 635, 636
Photo(chemo)therapy, 210
Phototoxic reactions, 286, 288, 294, 295, 305
Pigmentary disorders, 730–732
Pigment cells, 443
Pigmented purpuric dermatoses, 429
Pimecrolimus, 229, 448
Pityriasis, 78
Pityriasis lichenoides, 210
chronica (PLC), 208, 209
et varioliformis acuta (PLEVA), 208, 209
Pityriasis rubra, 78
Pityrosporum ovale, 369
Plain radiographs, 133
Plakin, 8–10
Porphyria acute intermittent porphyria (AIP), 469, 471, 472, 476, 477, 482, 483
acute porphyrias, 471, 473, 476–482, 484
congenital erythropoietic porphyria (CEP), 469–471, 473, 474, 478–481, 483
erthropoietic protoporphyria (EPP), 469, 470, 472, 474, 479, 480, 482, 483
hereditary coproporphyria (HCP), 469, 471, 472, 476, 480
nonscarring porphyrias, 471, 473–476, 478, 479, 481
porphyria cutanea tarda (PCT), 469–474, 476, 477, 479, 480
variegate porphyria (VP), 469, 471, 472, 476, 480, 482, 484
Porphyria, 105, 106
Porphyrogenic drugs, 478–481
Postherpetic neuralgia (PHN), 159
Post-kala-azar dermal leishmaniasis, 187
Poststreptococcal glomerulonephritis, 130
Potassium, 719
Potassium iodide, 462
Povidone-iodine, 745
p-Phenylene, 724
Prenatal flares, 363
Pressure ulcers (decubitus), 739
Prevention, 717, 722–723, 725, 729–730
  primary prevention, 279
  secondary prevention, 279
  tertiary prevention, 279
Primary cutaneous lymphoma
  primary cutaneous anaplastic large cell lymphoma (cALCL), 634
  primary cutaneous diffuse large B-cell lymphoma leg-type (PCDLBCL), 634
  primary cutaneous marginal zone lymphoma (PCMZL), 634, 640
Primary inoculation tuberculosis (PIT), 140, 141
Pro-drug, 22, 24, 26
Profilaggrin/filaggrin gene, 226
Promazine/chlorpromazine, 480, 481
Pro-opiomelanocortin (POMC)-derived peptides, 19
Prophylaxis, 36
Propionibacterium acnes, 360
Propionyl l-carnitines, 743
Propranolol, 699
Propylene glycol, 722
Prostaglandin E2 gel, 452
Prostaglandins, 19
Protease-activated receptor-2, 123
Proteases activated receptor 2 (PAR-2), 242
Proteases activated receptor 2 (PAR-2) antagonists, 243
Protein engineering, 748, 749
Protein-sulfonamide-compounds, 312
Proteinuria, 638
Proteoglycans, 6, 7
Protozoan infections
  amoebic infection, 184–185
  leishmaniasis and trypanosomiasis, 185–187
Provocation (test), 306, 307
Prurigo, 235, 327, 329–331
  nodularis, 236, 239–243
  simplex, 236
Prurigo of pregnancy (PP), 687–688
Pruritic dermatoses, 240
Pruritic folliculitis of pregnancy (PFP), 688–689
Pruritic urticarial papules and plaques of pregnancy (PUPPP), 685–687
Pruritus, 122–124, 227, 235–243, 679–682
  genitoanal pruritus, 240
  HES-induced pruritus, 241
  neurogenic pruritus, 241
  paraneoplastic pruritus, 242
  psychogenic pruritus, 242
Pseudocatalase, 448
Psoralen
  8-methoxypsoralen (8-MOP, methoxalen), 444–446
  (4,5,8-)trimethylpsoralen, 445
Psoralen plus ultraviolet A (PUVA), 80, 82, 195–199, 460, 462, 464, 635, 636
Psoriasis, 16
Psoriasis, 87–89, 208
  chronic plaque psoriasis, 80
  erythrodermic psoriasis, 80
  pustular psoriasis, 80
PUVASOL, 444, 445
Pyoderma faciale, 383
Pyoderma gangrenosum (PG), 337–339, 427, 740–744, 747
Pyoderma gangrenosum and aseptic arthritis
  (PAPA syndrome), 369
Pyodermas, 693
Q
Q-switched and long-pulsed laser systems, 99
Quality of life, 225, 227
Quinolone, 304, 305
R
Radiodermatitis, 637
Radiologists, 732
RANTES, 325, 329
Rash
  maculopapular rash, 697
  scarlatiniform rash, 697
  urticarial rash, 697
  viral rash, 693
Raynaud disease, 738
Raynaud’s phenomenon, 729, 730
Reactions
  allergic reactions, 298, 301
  anaphylactic reactions, 299
  A-type reactions, 297, 298
  B-type reactions, 298
  idiosyncrasy reactions, 298
  intolerance reactions, 298
  pseudoallergic reactions, 298, 299
Rebound phenomenon, 229
Recombinant human porphobilinogen deaminase (rhPBGD), 483
Reganex gel, 746
Regulatory T cells, 88
Reiter syndrome, 353–355
Relapsing polychondritis (RP), 351–353
Renal dysfunction, 322, 324
Repeated open application test (ROAT), 280
Resistance testing, 176, 178
Resveratrol, 615
Retiform parapsoriasis, 207
Retinaldehyde, 79–82
Retinoic acid (RA) metabolism blocking agents (RAMBAs), 82
  oral retinoid, 637
  retinoid therapy, 637
  retinoid X receptor, 637
Retinyl ester hydrolase (REH), 77
Reverse transcriptase, 173
Rhabdomyosarcoma, 664, 672
Rheumatoid arthritis, 730, 740, 741, 744
Rheumatoid neutrophilic dermatosis (RND), 344–345
Rheumatological diseases, 736
Rhino-conjunctivitis, 724
Rhomidepsin, 639
Rilpivirine, 176
Rituximab, 29–30, 36, 430, 640,
  erythromatotelangiectatic rosacea, 376–378, 381
  extrafacial rosacea, 376
fulminans rosacea, 383
granulomatous rosacea, 376, 378–380, 383
lupoid rosacea, 378
ocular rosacea, 376, 378, 382–383
papulopustular rosacea, 376, 378, 379, 381, 383
phymatous rosacea, 376, 378, 382
Rosacea-like tuberculid Lewandowsky, 378
Roxithromycin, 132
Rust inhibitors, 731
S
SAPHO syndrome, 363
Saquinavir, 176, 177
Sarcoidosis, 459–462, 465
Sarcopomtes scabiei, 183–184
Scabies, 694–696, 701
Scarring, 361, 368–370
Schönlein-Henoch Purpura, 427, 428
Scleroderma-like disorders, 730, 731
Sclerodermatous type, 434
Sclerotherapy, 743
Sclerotic features, 435, 436
Scrofuloderma (SD), 141
Sebaceous gland hyperplasia sebum (production), 360
Seborrheic dermatitis, 369
Sensitization, 275–276, 279
Serial dilution test, 280
Serine-threonine kinase mTOR, 673
Severe combined immunodeficiency, 577
Sezary syndrome (SS), 82, 634, 635, 637–640
Shave therapy, 745
Silicone derivatives, 363
Silvery hair syndromes, 586–587
Sirolimus, 438
Sjögren-Larsson syndrome, 566–567
Skin aging and photoaging
Botox, 710
CO2 laser treatment, 712
complications, 713–714
dermabrasion, 712
dermal fillers, 711–712
extracellular matrix alteration, 707–708
functional changes, 708
reactive oxygen species, 706–707
retinoids, 709–710
telangiectasia, 708
vitamin C, 710
Skin atrophy, 229, 231
Skin biopsy, 114–116
Skin cancer, 106–107
Skin equivalent, 745–747
Skin surface hydration, 60, 61
Small fiber neuropathy, 241
Soda lime, 719
Sodium
bicarbonate, 719
hypochlorite (bleach), 719
Solar lentigo, 526–527
Solar urticaria, 285–291
Specific dermatoses of pregnancy
herpes gestationis (HG), 682–695
prurigo of pregnancy (PP), 687–688
pruritic folliculitis of pregnancy (PFp), 688–689
pruritic urticarial papules and plaques of pregnancy
(PUPPP), 685–687
Spirolocalactone, 363, 367, 368
Sporotrichosis, 153–154
Squamous cell carcinoma (SCC), 637, 669–671
actinic keratoses (AKs), 609–610
Bowen’s disease, 610
cetuximab, 615
clinical variants, 611
human papillomavirus (HPV), 609
imiquimod, 613, 614
Mohs micrographic surgery, 613, 614
oral retinoids, 613
radiation therapy, 614
resveratrol, 615
tanning lamp usage, 609
Stanzolol, 463, 730
Staphylococcal scalded skin syndrome (SSSS)
biopsy, 136
exfoliative toxins, 136
Staphylococcus aureus, 129–131, 226, 230
Stavudine, 176
Stem cell biology, 748, 749
Steroid-induced acneiform eruption, 383
Steroids
systemic steroids, 462, 464, 465
topical corticosteroids, 460–462
Stevens-Johnson-syndrome (SJS), 301–304, 306, 309, 311
Stewart-Treves syndrome, 666
Stratum corneum (SC), 57–58
Strawberry tongue, 697
Streptomycin, 145
Subcorneal pustular dermatoses (SPD), 343–344
Sublingual immunotherapy (SLIT), 230
Substance P, 19, 241, 369
Sulfadiazine, 744
Sulfamethoxazole (SMX), 298, 312
Sulfonamide antimicrobials, 321, 323
Sulfonamide antimicrobials, 321, 323
Sulfur 5%, 379, 381
Sulphacetamide 10%, 379, 381
Sun protection, 452
Sun-protective clothing, 479, 480, 592, 593
Sunscreen, 379, 380
Superabsorbent polymers, 745, 748
Superficial muscular aponeurosis of the skin (SMAS), 541, 543
Superficial vein surgery, 743
Sweet’s syndrome (SS), 340–342
Sympathectomy, 521
Syndrome
Kasabach-Merritt syndrome, 698
PHACES syndrome, 698
SACRAL syndrome, 698
Synthetic occlusive dressings, 745
Syphilis, 169
Systemic corticosteroids, 410, 419
Systemic lupus erythematosus, 730
Systemic therapy
absolute and relative contraindications, 66–68
cytocrome P450 (CYP), 68–69
dermatology, 65
global variations, 75
glucose-6-phosphate dehydrogenase (G6PD), 70
medication adverse/side effect, 70
N-acetyltransferase (NAT), 69
patient education and informed consent, 65–66
pharmacologic principles, 63–64
polymorphisms, 68
potential drug interaction minimization, 70–73
stepwise approach, 64
thiopurine S-methyltransferase (TPMT), 69
toxicity monitor, 73–74
treatment regimen adjustments, 74

T
Tacalcitol, 448
Tacrolimus, 32, 36, 229, 437, 448, 460, 462, 463
Tactile sensitivity, 728
Tannin, 236
Tar, 732, 733
Tattooing, 452
Taxanes, 672
Tazarotene, 197, 364
Tazarotenic acid, 79, 81
TCDD (4-chlorinated tetra-chloro-dibenzo-dioxin), 724
T-cell depletion, 435–437
T-cells, 187
naive T-cells, 276
specific T-cells, 275–276
Telangiectasia, 445, 446, 708
Teratogenicity, 80, 83
Terbinafine, 150–155
Terbinfine, 513
Test
basophile activation test, 307, 310
epicutaneous testing, 277, 278, 280, 281
lymphocyte transformation test (LTT), 299, 304, 307, 310–314
patch-testing, 277, 278
in vitro test, 309, 310, 314
Testing systems
cellular testing systems, 310
serological testing systems, 304, 309–310
Tetracycline, 305, 363, 365–368
TGFβ, 325, 326
Thalidomide, 243, 460
Thiopurine S-methyltransferase (TPMT), 27, 69
Thrombocytopenia, 638, 640
Th1/Th0 pattern, 226
Thyroid disease, 461
Tinea
capitis, 149, 150
corparis, 149, 150
pedis, 149–150
unguim, 150
Tinea capitis, 693
Tissue edema, 728
Tissue therapies, 747
Tolerance, 18
Toll-like receptors (TLR), 15–16, 19, 226
Topical antifungal, 150, 152
Topical benzoyl peroxide, 363, 366
Topical chemotherapy, 635, 636
Topical corticosteroids, 635
Topical immunotherapy, 500–502
Topical/oral antibiotics, 129
Topical PUVA, 444, 446
Topical radiotherapy, 464
Topical retinoids, 382
Topical sunscreen, 479
Total-skin therapy
total-skin electron-beam radiotherapy, 635, 636
total-skin radiation therapy, 636–637
total-skin topical chemotherapy, 636
Toxicity
equivalents, 727
hepatotoxicity, 179
liver toxicity, 179
nephrotoxicity, 177, 179
Trachomatosis
Chlamydia trachomatis, 167, 168
Chlamydia trachomatis serotype, 168
Transcription factor HIF1 alpha, 698
Transepidermal water loss (TEWL), 58–61
Transilat, 460
Transplantation
allogeneic stem-cell transplantation, 481
bone marrow transplantation, 480–482
liver transplantation, 480, 482
Tregs, 226
Treponema pallidum
hemagglutination test (TPHA), 165, 166
particle agglutination test (TPPA), 165, 166
Tretinoin, 364–366
alitretinoin, 80
isotretinoin, 78–80
Trichophyton rubrum, 512
Trichothiodystrophy (TTD), 591–592
Triclosan, 229, 230
Trigger factors, 228
Trimethoprim, 298, 301
Tuberculosis verrucosa cutis (TVC), 140, 141
Tularemia, 144–146
Tumor angiogenesis, 673
Tumor necrosis factor, 18
Tumor necrosis factor-α (TNF-α), 29, 32–34, 36
blockade, 744
antagonists, 300, 312
Tyrosine-kinase receptor, 661
Tzanck smear, 158

U
Ulcerative colitis, 740
Ulcus cruris venosum, 737, 739, 744
Urea, 236
Urethritis, 167, 168, 170
Ursodeoxycholic acid (UDCA), 680
Urticaria, 247–261
Urticaria pigmentosa, 265–267
UVA1, 89–90
VAC therapy system, 748
Vaginal candidiasis, 368
Varicella and zoster virus (VZV), 158–159
Varicella zoster immune globlin (VZIG), 159
Vascular endothelial factor growth, 673
Vascular malformations
  clinical characteristics and diagnosis, 647–650
  endovascular embolization, 655
  etiology and pathogenesis, 643–647
  flash lamp pumped pulsed dye laser, 651–652
  photoderm VL, 652
  potential extracutaneous association, 651
Vascularitis, 736, 738, 741, 742, 744
VEGF, 746
Veneral disease research laboratory (VDRL), 165
Venous angioma, 645
Venous insufficiency, 736, 738, 743
Venous malformations (VMs), 645, 649–650, 652–654
Vermilion border, 59
Verruca vulgaris, 693
Vesiculopustules, 129
Vibration
  hand-arm vibration syndrome, 728–730
  vibration white finger, 728–730
Vicriviroc, 176
Vinblastine, 701
Vincaalkaloids, 672
Vincristine, 672, 699
Viral infections
  hand, foot, and mouth disease (HFMD), 161–162
  herpes simplex, 157–158
  human papillomavirus (HPV), 160
  molluscum contagiosum (MC), 160–161
  varicella and zoster, 158–159
Virus, 215, 216
Vitamin A, 77, 78, 83
Vitamin C, 710
Vitiligo, 533–535, 694, 695, 702
  generalized vitiligo, 443, 452
  segmental vitiligo, 443, 444
  vulgaris vitiligo, 443
Vorinostat, 639, 640
Water-binding capacity, 60
Wet-to-dry treatment, 745
Williams-Beuren syndrome, 48
Wiskott-Aldrich Syndrome (WAS), 580–581
World Health Organization (WHO) classification, 633, 634
Wound care centers, 742
Wound healing, 735–750
Xanthoma, 489–490
Xantoerythroderma perstans, 207
Xeroderma pigmentosum, 695
Xeroderma pigmentosum (XP), 590–594
X-linked dominant inheritance, 45
X-linked recessive inheritance, 45–46
X-ray technician, 732
Yellow and green light lasers, 99–100
Zafirlukast, 241
Zalcitabine, 176
Ziehl-Neelsen staining, 139
Zileuton, 241
Zostavax vaccine, 159