John C. Hall
Brian J. Hall *Editors*

Cutaneous Drug Eruptions

Diagnosis, Histopathology and Therapy

Springer

Cutaneous Drug Eruptions

John C. Hall • Brian J. Hall
Editors

Cutaneous Drug Eruptions

Diagnosis, Histopathology and Therapy

Springer

Editors
John C. Hall
Kansas City
Kansas
USA

Brian J. Hall
Miraca Life Sciences
Irving
Texas
USA

ISBN 978-1-4471-6728-0 ISBN 978-1-4471-6729-7 (eBook)
DOI 10.1007/978-1-4471-6729-7

Library of Congress Control Number: 2015949115

Springer London Heidelberg New York Dordrecht

Printed on acid-free paper

Springer-Verlag London Ltd. is part of Springer Science+Business Media (www.springer.com)

For the wonderful authors who made this book a reality
and the patients to whose care they are so selflessly dedicated.
Thank you also to the patients who graciously allowed their
photographs to be used so this book could come to fruition.

Introduction

Use of medications in the population as a whole is increasing, and as the baby boomer cohort ages, more people will survive with chronic illnesses, and with new medical advances, there is an ever-increasing transplant population. One of the most difficult aspects of polypharmacy is allergic and toxic reactions to drugs. The skin is often the only or the earliest harbinger of multi-organ system damage in these patients. The skin is also the most easily observed and biopsied.

Therefore, a textbook covering all aspects of this challenging dilemma seems apropos. That is what this treatise attempts to do. And in so doing, we hope to create an accessible resource for early detection and resolution of cutaneous drug reactions.

Kansas City, MO, USA — John C. Hall, MD
Irving, TX, USA — Brian J. Hall, MD

Contents

Part I The Skin and Drug Interactions

1 Immunology of Cutaneous Drug Eruptions 3
Jon A. Dyer

2 Principles of Diagnosis of Cutaneous Drug Eruptions 13
John C. Hall

3 Histopathology of Drug Reactions 17
Brian J. Hall and Beth Ruben

4 Principles of Treatment of Cutaneous Drug Eruptions 33
Cindy E. Owen and Jeffrey P. Callen

Part II Drug Skin Reactions and Clinical Subgroups

5 Morbilliform Drug Eruptions 45
Uzoamaka T. Ukoha, Amit G. Pandya, and Arturo R. Dominguez

6 Drug-Induced Urticaria 55
Tarek S. Shaath, Vikas K. Patel, Anand N. Rajpara, Garth R. Fraga, and Daniel J. Aires

7 Erythema Multiforme and Drug Reactions 65
Eric Dean Merrill and Carol W. Stanford

8 Drug-Induced Vasculitis 77
Shelly Rivas, Amit G. Pandya, and Arturo R. Dominguez

9 Pigment Changes and Drug Reactions 87
Shinjita Das and A. Shadi Kourosh

10 Drug-Induced Photosensitivity 107
Liza Gill and Henry W. Lim

11 Erythema Nodosum as a Drug Eruption 123
Shilpi Khetarpal and Wilma F. Bergfeld

12 Lichen Planus Drug Reactions 129
Carol W. Stanford and Kaitlin Vogt Schiavo

13 Pityriasis Rosea-Like Drug Eruptions 135
Kaitlin Vogt Schiavo and Carol W. Stanford

14 Psoriasiform Drug Eruptions and Drugs That Flare Psoriasis 141
Elizabeth B. Lester, Deborah L. Cook, and Gretchen W. Frieling

15 Acne and Drug Reactions 157
Christopher P. Schiavo and Carol W. Stanford

16 Collagen Vascular Diseases and Cutaneous Drug Reactions 167
Ritika Trikha, Helena R. Winston, Lindsay N. Boyers, and Chante Karimkhani

17 Fixed Drug Eruptions 181
Kara M. Pretzlaff, Amit G. Pandya, and Arturo R. Dominguez

18 Autoimmune Bullous Diseases and Drugs 193
Margaret A. Stafford, Shivani S. Patel, Lindsay N. Boyers, and Chante Karimkhani

19 Lymphoma and Pseudolymphoma and Drug Reactions 205
Matthew Hoffmann

Part III Drug Reactions of the Appendeges

20 Drug-Induced Alopecia 215
Kendra Lesiak, Jamen R. Bartlett, and Gretchen W. Frieling

21 Drug Eruptions of the Scalp 229
Wilma F. Bergfeld and Shilpi Khetarpal

22 Drug Reactions in the Nail in Cutaneous Drug Eruptions 235
John P. Scopetta, Dipti Anand, Antoanella Calame, and A. Shadi Kourosh

Part IV Life-Threatening Skin Drug Reactions

23 Drug Eruptions and Erythroderma 251
Yuri T. Jadotte, Robert A. Schwartz, Chante Karimkhani, Lindsay N. Boyers, and Shivani S. Patel

24 Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis 259
Natasha Klimas, Josephine Quintanilla-Dieck, and Travis Vandergriff

25 Drug-Induced Delayed Multi-organ Hypersensitivity Syndrome 271
Natasha Klimas, Josephine Quintanilla-Dieck, and Travis Vandergriff

26 Acute Generalized Exanthematous Pustulosis 281
Jonathan J. Lee, Daniela Kroshinsky, and Mai P. Hoang

Part V Skin Drug Reactions of Specific Drug Groups

27 Cutaneous Drug Reactions to Anticoagulants 293
Sarah A. Fantus

28 Antiepileptic Medications and Cutaneous Drug Reactions . . . 301
Sarah A. Fantus

29 Chemotherapy and Cutaneous Drug Reactions. 309
Gabriella Fabbrocini, Luigia Panariello, Gemma Caro, and Giuseppe Monfrecola

30 Tyrosine Kinase Medications and the Skin 323
Emily Y. Chu

31 Medical Therapies and Their Effects on Skin Cancer 333
Man Kin D. Ho and Noah S. Scheinfeld

32 Cutaneous Reactions to BRAF Inhibitors 341
Holly H. McCoppin

33 Cutaneous Reactions to Corticosteroids. 353
Eleanor J. Feldman

34 Cutaneous Reactions to Retinoids. 361
Gretchen W. Frieling and Andrew R. Tegeder

Part VI Cutaneous Reactions with Specific Pathology

35 Neutrophilic Dermatoses 375
Cassondra M. Andreychik and Dirk M. Elston

36 Granulomatous Drug Reactions 389
Kathleen A. Long

Part VII Drug Reactions in Specific Populations

37 Cutaneous Drug Reactions in Patients Infected with Human Immunodeficiency Virus. 397
James F. Stanford

38 Pediatric Drug Eruptions of the Skin 431
Gretchen W. Frieling

Index 445

Contributors

Daniel J. Aires, MD, JD Division of Dermatology, University of Kansas School of Medicine, Kansas City, KS, USA

Dipti Anand Managing Director, SkinPath SolutionsSmyrna, GA, USA

Cassondra Andreychik, BA The Commonwealth Medical College, Scranton, PA, USA

Jamen R. Bartlett, MD Pathology, The University of Vermont Medical Center, Burlington, VT, USA

Wilma F. Bergfeld, MD Dermatopathology, Cleveland Clinic, Cleveland, OH, USA

Lindsay N. Boyers, BA Georgetown University School of Medicine, Washington, DC, USA

Antoanella Calame, MD Department of Dermatology and Dermatopathology, Compass Dermatopathology, San Diego, CA, USA

Jeffrey P. Callen, MD Division of Dermatology, University of Louisville School of Medicine, Louisville, KY, USA

Gemma Caro, MD Division of Clinical Dermatology, Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy

Emily Y. Chu, MD, PhD Dermatology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Deborah L. Cook, MD Department of Pathology and Laboratory Medicine, University of Vermont College of Medicine/Fletcher Allen Health Care, Burlington, VT, USA

Shinjita Das, MD Department of Dermatology, Massachusetts General Hospital, Boston, MA, USA

Arturo R. Dominguez, MD Department of Dermatology, University of Texas Southwestern Medical Center, Dallas, TX, USA

Jonathan A. Dyer, MD Dermatology and Child Health, University of Missouri, Columbia, MO, USA

Dirk M. Elston, MD Ackerman Academy of Dermatopathology, New York, NY, USA

Gabriella Fabbrocini, PhD Division of Clinical Dermatology, Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy

Sarah A. Fantus, MD Internal Medicine, Loyola University Medical Center, Maywood, IL, USA

Eleanor J. Feldman, BA Dermatology, SUNY Downstate Medical Center, Brooklyn, NY, USA

Garth R. Fraga, MD Department of Pathology and Laboratory Medicine, University of Kansas School of Medicine, Kansas City, KS, USA

Gretchen W. Frieling, MD Pathology, The University of Vermont, Burlington, VT, USA

Kayla A. Gertsema, MD Department of Child & Adolescent Psychiatry, UT Austin, Austin, TX, USA

Liza Gill, BS Department of Dermatology, Henry Ford Medical Center–New Center One, Detroit, MI, USA

Brian J. Hall, MD Pathology, Miraca Life Sciences, Irving, TX, USA

John C. Hall, MD Dermatology, Organisation Name, Kansas City, MO, USA

Man Kin D. Ho, BS College of Medicine, SUNY Downstate Medical Center, Brooklyn, NY, USA

Mai P. Hoang, MD Department of Pathology, Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA

Matthew Hoffmann, MD Department of Dermatology, LSU Health New Orleans, New Orleans, LA, USA

Yuri T. Jadotte, MD Division of Nursing Science and Department of Quantitative Methods, Epidemiology and Biostatistics, Rutgers University School of Nursing and Rutgers University School of Public Health, Newark, NJ, USA

Joseph L. Jorizzo, MD Clinical Dermatology, Weill Cornell Medical College, New York, NY, USA

Chante Karimkhani, BA Columbia University College of Physicians and Surgeons, New York, NY, USA

Shilpi Khetarpal, MD, BS Dermatology, The Cleveland Clinic Foundation, Cleveland, OH, USA

Natasha Klimas, BS Department of Dermatology, University of Texas Southwestern Medical Center, Dallas, TX, USA

A. Shadi Kourosh, MD Department of Dermatology, Massachusetts General Hospital, Boston, MA, USA

Harvard Medical School, Boston, MA, USA

Daniela Kroshinsky, MD, MPH Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Jonathan J. Lee, BA Department of Pathology, Harvard Medical School, Boston, MA, USA

Kendra Lesiak, MD, MEd Division of Dermatology, University of Vermont Medical Center, Burlington, VT, USA

Elizabeth B. Lester, MD Dermatology, University of Vermont, Burlington, VT, USA

Henry W. Lim, MD Department of Dermatology, Henry Ford Medical Center–New Center One, Detroit, MI, USA

Kathleen A. Long, BS Department of Dermatology, University of Missouri–Columbia, Columbia, MO, USA

Holly H. McCoppin, MD Dermatology, College Park Family Care Center, Overland Park, KS, USA

Dermatology University of Kansas Medical Center, Kansas City, KS, USA

Eric Dean Merrill, BA, MD School of Medicine, University of Missouri–Kansas City, Kansas City, MO, USA

Guiseppe Monfrecola, PhD Division of Clinical Dermatology, Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy

Thomas Nicotri Jr., MD Department of Dermatology, LSUHSC Dermapathology, Louisiana, USA

Cindy E. Owen, MD, MS Division of Dermatology, University of Louisville, Louisville, KY, USA

Luigia Panariello, MD Division of Clinical Dermatology, Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy

Amit G. Pandya, MD Department of Dermatology, University of Texas Southwestern Medical Center, Dallas, TX, USA

Shivani S. Patel, BA, BS College of Medicine, Medical University of South Carolina, Charleston, SC, USA

Vikas K. Patel, MD Department of Dermatology, Kansas University Medical Center, Kansas City, KS, USA

Kara M. Pretzlaff, BA Dermatology, UT Southwestern Medical School, Dallas, TX, USA

Josephine Quintanilla-Dieck, MD Department of Dermatology, University of Texas Southwestern Medical Center, Dallas, TX, USA

Anand N. Rajpara, MD Dermatology, The University of Kansas Medical Center, Kansas City, KS, USA

Shelly Rivas, MD Internal Medicine, Yale–New Haven Hospital, New Haven, CT, USA

Beth Ruben, MD Dermatology and Pathology, University of California, San Francisco, San Francisco, CA, USA

Noah S. Scheinfeld, MD, JD Department of Dermatology, Weil Cornell Medical College, New York, NY, USA

Christopher P. Schiavo, BA Department of Internal Medicine, University of Missouri–Kansas City School of Medicine, Kansas City, MO, USA

Robert A. Schwartz, MD, MPH, DSc (Hon) Dermatology, Pediatrics, Medicine, and Preventive Medicine and Community Health, Rutgers University New Jersey Medical School and Rutgers University School of Public Affairs and Administration, Newark, NJ, USA

John P. Scopetta, MD Pathology, Tulane University, New Orleans, LA, USA

Tarek S. Shaath, BA, MD The University of Kansas School of Medicine, The University of Kansas Medical Center, Kansas City, KS, USA

Margaret A. Stafford, BA College of Medicine, Medical University of South Carolina, Charleston, SC, USA

Carol W. Stanford, MD, FACP Department of Internal Medicine, University of Missouri–Kansas City School of Medicine, Kansas City, MO, USA

James F. Stanford, MD, FACP Infection Prevention and Control, Department of Medicine, Section of Infectious Diseases, Truman Medical Center, University of Missouri – Kansas City School of Medicine, Kansas City, MO, USA

Andrew R. Tegeder, MD, MS Dermatology, University of Vermont, Burlington, VT, USA

Ritka Trikha, BS Rosalind Franklin University of Medicine and Science, North Chicago, IL, USA

Uzoamaka T. Ukoha, BS Department of Dermatology, University of Texas Southwestern, Dallas, TX, USA

Travis W. Vandergriff, MD Dermatology and Pathology, UT Southwestern Medical Center, Dallas, TX, USA

Kaitlin Vogt Schiavo, BA School of Medicine, University of Missouri–Kansas City, Kansas City, MO, USA

Helena R. Winston, MSc, MPhil, BA University of Colorado School of Medicine, Aurora, CO, USA

Abbreviations

5-MOP	5 methoxypsoralen
6-MP	6-mercaptopurine
6-TG	6-thioguanine
AA	Arachidonic acid
ABCD	Acquired brachial cutaneous dyspigmentation
ACE	Angiotensin converting enzyme [inhibitor]
ACE-I	Angiotensin-converting enzyme inhibitors
ADR(s)	Adverse drug reaction(s)
AE	Anagen effluvium
AED(s)	Antiepileptic drug(s)
AEs	Adverse effects
AGA	Androgenetic alopecia
AGEP	Acute generalized exanthematous pustulosis
AHEI	Acute hemorrhagic edema of infancy
AIN	Acute interstitial nephritis
ALT	Alanine aminotransferase
AML	Acute myelogenous leukemia
ANA	Antinuclear antibody
ANCA	Anti-neutrophil cytoplasmic autoantibodies/antibodies/ antibody
ARBs	Angiotensin receptor blockers
ARDS	Acute respiratory distress syndrome
ARS	Acute retroviral syndrome
AST	Aspartate aminotransferase
AZA	Azathioprine
BCC	Basal cell carcinoma
BP	Bullous pemphigoid
BPAg2	Bullous pemphigoid antigen 2
BPL	As B-cell lymphoma-like pseudolymphoma
BRAF	Rapidly accelerated fibrosarcoma kinase B
BSA	Body surface area
BUN	Blood urea nitrogen
CAD	Chronic actinic dermatitis
cADRs/CDARs	Cutaneous adverse drug reactions
c-AMP	Cyclic-AMP
CAPS	Cryopyrin-associated periodic syndrome
CCB(s)	Calcium channel blocker(s)

CD	Crohn's disease
CIA	Chemotherapy-induced alopecia
CLA	Cutaneous lymphocyte-associated antigen
CML	Chronic myelogenous leukemia
CMV	Cytomegalovirus
COX	Cyclooxygenase
CPK	Creatine phosphokinase
CPL	Cutaneous T-cell lymphoma-like pseudolymphoma/ cutaneous pseudolymphoma
CREST	Calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, teleangiectasias
CRP	C-reactive protein
CSF(s)	Colony-stimulating factor(s)
CSS	Churg-Strauss syndrome
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	Cutaneous T-cell lymphoma
cuSCCs	Keratoacanthomas-type squamous cell carcinomas
CVD	Collagen vascular diseases
DFSP	Dermatofibrosarcoma protuberans
DH	Dermatitis herpetiformis
DHS	Drug hypersensitivity syndrome
DIBP	Drug-induced bullous pemphigoid
DIDMOHS	Drug-induced delayed multi-organ hypersensitivity
DIEM	Drug-induced erythema multiforme
DIF	Direct immunofluorescence
DIHS	Drug-induced hypersensitivity syndrome
DIV	Drug-induced vasculitis
DLE	Discoid lupus erythematosus
DM	Dermatomyositis
DMARD	Disease-modifying antirheumatic drug
DMT1	Type 1 diabetes mellitus
DNA	Deoxyribonucleic acid
DRESS	Drug rash/reaction with eosinophilia and systemic symptoms
Dsg-1	Desmoglein 1
Dsg-3	Desmoglein 3
DTH	Delayed-type hypersensitivity
DVT	Deep-vein thrombosis
EBA	Epidermolysis bullosa acquisita
EBV	Epstein-Barr virus
ECMO	Extracorporeal membrane oxygenation
EED	Erythema elevatum diutinum
EGFR(s)	Epidermal growth factor receptor(s)
EGFRi	Epidermal growth factor receptor inhibitors
EM	Erythema multiforme
EMG	Electromyography
EMPACT	Erythema multiforme associated with phenytoin/ phenobarbital and cranial radiation therapy
EN	Erythema nodosum

EPDS	Erosive pustular dermatosis
EPF	Eosinophilic pustular folliculitis
ESR	Elevated erythrocyte sedimentation rate
FcεRI	High-affinity IgE Fc receptor
FDC	Fixed-dose combination
FDE(s)	Fixed drug eruption(s)
GBFDE	Generalized bullous FDE
G-CSF	Granulocyte colony stimulating factors
GIST	Gastrointestinal stromal tumor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GnRH	Gonadotropin-releasing hormone
GPA	Granulomatosis with polyangiitis
GPP	Generalized pustular psoriasis
GVHD	Graft-versus-host disease
H & E	Hematoxylin and eosin [stain]
HAART	Highly active antiretroviral therapy
HAEM	HSV-associated EM/herpes-associated EM
HCTZ	Hydrochlorothiazide
HCV	Hepatitis C virus
HER	Human epidermal receptor
HFS	Hand–foot syndrome
HHV	Human herpes virus
HISN	Heparin-induced skin necrosis
HIT	Heparin-induced thrombocytopenia
HITT	Heparin-induced thrombocytopenia and thrombosis
HL	Hodgkin's lymphoma
HLA	Human leukocyte antigen
HPLC	High-pressure liquid chromatography
HSV	Herpes simplex virus
IBD	Inflammatory bowel disease
IFN(s)	Interferon(s)
IGDR	Interstitial granulomatous drug reaction
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IRIS	Immune response inflammatory syndrome
IRS	Immune reconstitution syndrome
ISH	In situ hybridization
IVIG	Intravenous immunoglobulin
J-SCAR	Japanese Research Committee on Severe Cutaneous Adverse Reaction
KS	Kaposi sarcoma
LABD	Linear IgA bullous dermatosis
LCV	Leukocytoclastic vasculitis
LDH	Lactate dehydrogenase
LINA	Linear IgA
LMWHs	Low-molecular-weight heparins
LTT	Lymphocyte transformation test

MAPK	Mitogen-activated protein kinase
MAR	Medical administration record
MBI	Mucosal barrier injury
MCD	Mast cell degranulation [test]
MED	Minimal erythema dose
MF	Mycosis fungoides
MIAN	Methotrexate-induced accelerated nodulosis
MKi	Multikinase inhibitors
MMF	Mycophenolate mofetil
MPA	Microscopic polyangiitis
MRSA	Methicillin-resistant staphylococcus aureus
MSH	Melanocyte-stimulating hormones
MTX	Methotrexate
NAC	N-acetylcysteine
nbUVB	Narrow-band ultraviolet-B
NEH	Neutrophilic eccrine hidradenitis
NMSC	Non-melanoma skin cancer
NPFDE(s)	Non-pigmenting fixed drug eruption(s)
NSAIDs	Nonsteroidal anti-inflammatory drugs/anti-inflammatories
OCPs	Oral contraceptive pills
OI(s)	Opportunistic infection(s)
P	Perinuclear
PAN	Polyarteritis nodosa
pANCA	Perinuclear antineutrophilic cytoplasmic antibodies
PCR	Polymerase chain reaction
PCT	Porphyria cutanea tarda
PDGFR	Platelet-derived growth factor receptor
PEP	Post-exposure prophylaxis
PF	Pemphigus foliaceus
PF4	Platelet factor 4
PG	Pyoderma gangrenosum
PMLE	Polymorphous light eruption
PNGD	Palisaded neutrophilic granulomatous dermatitis
PNP	Paraneoplastic pemphigus
PR3	Proteinase 3
PSAI	Psoriasis area severity index
PTU	Propylthiouracil
PUVA	Psoralen plus ultraviolet A/plus UVA
PV	Pemphigus vulgaris
RA	Rheumatoid arthritis
RAAST	Radioallergosorbent test
RAF	Rapidly accelerated fibrosarcoma kinase
RANTES	Regulated on activation, normal T expressed and secreted
Rapa	Rapamycin
RegiSCAR	[European] Registry of Severe Cutaneous Adverse Reaction
RND	Rheumatoid neutrophilic dermatitis
ROS	Reactive oxygen species
SCAR(s)	Severe cutaneous adverse reaction(s)

SCC	Squamous cell carcinoma
SCF	Stem cell factor
SCLE	Subacute cutaneous lupus erythematosus
SDRIFE	Symmetrical drug-related intertriginous and flexural exanthema
SIRS	Systemic inflammatory response syndrome
SJS	Stevens-Johnson syndrome
SLE	Systemic lupus erythematosus
SSLR	Serum sickness-like reaction
SSRI	Selective serotonin reuptake inhibitor
TE	Telogen effluvium
TEN	Toxic epidermal necrolysis
TEN/SJS	Toxic epidermal necrolysis/Stevens-Johnson Syndome
TNF	Tumor necrosis factor
TPL	T-cell lymphoma-like pseudolymphoma
TPMT	Thiopurine-S-methyltransferase
Treg	Regulatory T [cells]
TTP	Thrombotic thrombocytopenic purpura
UFH	Unfractionated heparin
UV	Ultraviolet
UVA	Ultraviolet A
UVB	Ultraviolet B
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WISN	Warfarin-induced skin necrosis
ZVD	Zidovudine

Part I

The Skin and Drug Interactions

Immunology of Cutaneous Drug Eruptions

1

Jon A. Dyer

Abstract

Adverse drug reactions (ADRs) are divided into type A (pharmacotoxicologic) and type B (hypersensitivity) reactions. Type B ADRs represent ~10–15 % of all ADRs, and immune-mediated hypersensitivity drug reactions account for ~10 % of type B ADRs. These hypersensitivity reactions are reproducible with repeat drug exposure and occur at drug dosages tolerated by normal patients. The immune mechanisms leading to type B severe cutaneous adverse reactions to drugs (SCARs) are diverse and incompletely understood. Ongoing research is shedding some light on these diverse reaction patterns, but also generating new questions. While the human immune system functions as a seamless syncytium, the intellectual compartmentalization of the immune system into various "arms" makes it easier to comprehend. Certain of these arms appear to predominate in the various types of SCARs noted clinically.

Keywords

Pharmacotoxilogic • Pharmacogenetic • Pharmacoepegenitic • Human leukocyte antigen (HLA) • Haplotypes • Hapten • Hapten independent model • Altered peptide repetoire model • Prohapten • T-cells • T-cell receptor (TCR) • Severe cutaneous adverse reactions (SCARs) • Adverse drug reactions (ADR)

Adverse drug reactions (ADRs) are divided into type A (pharmacotoxicologic) and type B (hypersensitivity) reactions. Type B ADRs represent ~10–15 % of all ADRs, and immune-mediated hypersensitivity drug reactions account for ~10 % of type B ADRs. These hypersensitivity reactions are reproducible with repeat drug exposure and occur at drug dosages tolerated by normal patients. The immune mechanisms leading to type B severe cutaneous adverse reactions to drugs (SCARs) are diverse and incompletely understood. Ongoing research is shedding some light on these diverse reaction patterns, but also generating new

J.A. Dyer
Department of Dermatology and Child Health,
University of Missouri, 1 Hospital Dr,
Room MA111D, Columbia, MO 65212, USA
e-mail: dyerja@health.missouri.edu

J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_1

Table 1.1 Gel and Coombs Hypersensitivity reactions

		Mediator	Mechanism(s)	Clinical phenotypes
Type I	Immediate	IgE	Ag binding to mast cell/ basophil surface receptors	Urticarial, anaphylaxis, angioedema
Type II	Antibody-mediated (cytotoxic)	IgM, IgG	Ab binds to Ag leading to complement driven cell lysis or cell-mediated cytotoxicity or recruitment of neutrophils/ monocytes	Goodpasture's; ANCA vasculitis; drug-induced thrombocytopenia; hemolytic anemia
Type III	Immune complex	IgM, IgG, IgA	Ag-Ab complexes deposit in tissue – trigger recruitment of leukocytes and activation	Serum sickness reaction; Henoch-Schönlein purpura
Type IV	Delayed-type	T-lymphocytes	Activated T cells produce cytokines causing inflammation leading to tissue effects or directly attack cells	
	Type IVa Monocytic	Th1 CD4+: IFN-γ, TNF	IFN-γ stimulated KC and MC cytokine production	Allergic contact dermatitis
	Type IVb Eosinophilic	Th2 CD4+: IL-4, IL-5, IL-13	Th2 cytokines and eotaxin recruit eosinophils	DIHS
	Type IVc Cytotoxic T cells	Cytotoxic CD8+ or CD4+ T cells: IFN-γ; TNF	Activated cytotoxic T cells induce KC lysis	SJS/TEN
	Type IVd Neutrophilic	Th17 CD4+: IL-17, IL-22, IL-8	Th17 cell derived IL-17/IL-22 stimulate KC secretion of IL-8 leading to neutrophil recruitment	AGEP

questions. While the human immune system functions as a seamless syncytium, the intellectual compartmentalization of the immune system into various "arms" makes it easier to comprehend. Certain of these arms appear to predominate in the various types of SCARs noted clinically.

Both adaptive and innate aspects of the immune system may contribute to the development of SCARs. The classic Gel and Coombs delineation of delayed type hypersensitivity reactions highlights recognized mechanisms that lead to the development of different SCARs (Table 1.1).

Genetic factors have long been recognized to have a strong contributory role, and with improvements in genetic analysis, the mechanisms by which specific inherited polymorphisms contribute to specific SCARs are being clarified. This has led to the development of the fields of pharmacogenetics and pharmacogenomics. Further elucidation of these mechanisms may lead to the development of pharmacoepigenomics/pharmacoepigenetics as better understanding of the effect of environmental factors on the genome leading to predisposition or resistance to SCARs is understood. Genetic factors influence the development of SCARs in a variety of ways. Inherited variations in drug-metabolizing enzymes may increase the production of immunogenic drug metabolites (variable metabolism by variants of cytochrome p450 enzymes or altered drug processing by variations in epoxide hydrolase). Additionally, specific haplotypes of human leukocyte antigen (HLA), which play a primary role in T cell stimulation, have long been recognized to contribute to increased risk of SCARs.

Genetic factors, drug pharmacology, and immune responses interact in complex fashions to create the potential for SCARs. Better understanding of these interactions and how they lead to SCARs will lead not only to improved therapeutic interventions, but also allow pharmacogenomic testing to preemptively assess patients for risk of reactions to specific drugs.

Models of Drug Allergy Development

Several models exist to explain how MHC-dependent T-cell stimulation by drugs develops, triggering the immune responses that leads to SCARs.

The classic *hapten/prohapten model* proposes that a small neutral molecule becomes immunogenic upon binding to a protein. There are various mechanisms by which this could develop; a small molecule binding to a high molecular weight protein then becomes immunogenic. Prohapten molecules can become immunogenic after metabolism to intermediates that are reactive and can then bind to proteins. This allows presentation via HLA molecules to T cells and development of an immune response. After re-exposure, memory T cells proliferate, triggering an inflammatory response over 24–72 h.

A second mechanism is the *hapten independent* (*p-i model*) where direct interaction of the drug with immune receptors occurs without a prior sensitization phase. The interaction is directly with T cell receptors or MHC molecules and can explain how some drugs trigger T cell activation without prior exposure. A final concept, *the altered peptide repertoire model*, suggests that an altered milieu of self-peptides is presented to or recognized by T cells due to drug binding in the antigen-binding cleft of certain HLA molecules thus triggering the immune response. This is exemplified by abacavir, which appears to non-covalently bind in the F-pocket of HLA-B*5701 altering the shape of the cleft and the peptides that bind it.

Pharmacogenetics

An increased risk of SCARs in association with specific HLA types has long been recognized. Table 1.2 summarizes better-known associations and their representative populations.

The recognition of these associations has led to pharmacogenetic screening for high-risk alleles. Examples include screening for HLA-B*5701 in patients to be treated with abacavir, and the drug should not be used in patients who carry HLA-B*5701. For allopurinol, screening for HLA-B*5801 is recommended in high-risk populations, such as those with Han Chinese or Thai descent. Genetic screening for the HLA-B*1502 allele in patients with Asian ancestry is recommended prior to starting carbamazepine and it should not be used if the allele is present. A variety of studies have demonstrated the cost effectiveness of screening for these known alleles in high-risk populations (Asia) and HLA-B screening is performed prior to initiation of abacavir, allopurinol, and carbamazepine in Thailand.

Inherited variations in other systems important to the immune response (8- TCR subtypes) or metabolism of drugs in the skin (skin specific metabolic enzymes) may also play predisposing roles in the development of SCARs. While most drug metabolism occurs in the liver with few metabolites reaching the skin, drug-metabolizing enzymes do exist in the skin including some that are skin specific. While genetic variations in these enzymes and associated variation in risk of drug reactions has not been extensively studied it is an area of ongoing research.

A comprehensive review of basic immunology is beyond the scope of this chapter, and specific types of SCARs will be reviewed later in this volume. However, several SCARs will be briefly mentioned to highlight basic concepts in immunology leading to adverse reactions. The reader is referred to specific chapters for more detail on the clinical aspects and treatments of these conditions.

Stevens-Johnsons Syndrome/Toxic Epidermal Necrolysis (SJS-TEN)

Stevens-Johnsons syndrome/Toxic epidermal necrolysis (SJS-TEN) is one of the most feared SCARs. SJS/TEN is a type IVc hypersensitivity reaction where aberrant T cell activation triggers keratinocyte (KC) death and variable amounts of epidermal detachment. While specifics of this aberrant immune response in SJS/TEN are the subject of ongoing investigation, CD8+ cytotoxic T cells play a primary role. This is in contrast to the more common maculopapular drug exanthems, which account for ~90 % of drug eruptions, where cytotoxic CD4+ T cells are implicated. For T cell degranulation to occur there must be direct contact between T cells and antigen presenting cells (APCs) and the T cell receptor (TCR) must recognize specific antigen (Ag) bound to MHC. Granulysin released from degranulating cytotoxic T cells is likely a key player in the clinical findings of SJS/TEN.

Table 1.2 HLA haplotypes associated with cutaneous drug reactions

Drug	Allele	Population	Clinical syndrome	OR (95 % CI)	*P*-value	FDA Recommended Genetic Testing	Reference
Abacavir	HLA-B*5701	Australian	DIHS	117 (29–481)	<0.0001		22
		US European	DIHS	1945 (110–34,352)		Yes	23
		US African	DIHS	900 (38–21,045)		Yes	23
Allopurinol	HLA-B*5801	Han, Korean, Thai, European	SJS-TEN	96.6 (24–381)	<0.001	No	24
		Han		580 (34–9781)	4.7×10^{-24}		25
		Thai	SJS-TEN	348 (19–6337)	1.6×10^{-13}	No	26
		Korean	SJS-TEN	179 (10.2–3152)		No	27
		Korean	DIHS	161 (18–1430)	1.45×10^{-10}	No	28
Carbamazepine	HLA-B*1502	Canadian	SJS-TEN	38.6 (2.7–2240)	0.002		29
		Han, Thai, Malaysian	SJS-TEN	113 (51–251)	$<1\times10^{-5}$	Yes	30
		Han, Thai, Malaysia, Korean	SJS-TEN	80 (28–224)	0.07	Yes	31
	HLA-A*3101	Han	DIHS	12 (3.6–41)	0.002	Warning	32
		Korean	DIHS; SJS-TEN	12 (4.5–34); 6.5 (1.4–30)	2.9×10^{-6}; 0.03	Warning	33
		Japanese	SJS-TEN	16 (4.8–56)	0.0004	Warning	34
		European	DIHS; SJS-TEN	12.4 (1.3–121); 26 (5–116)	0.03; 8×10^{-5}	Warning	35
		Han, Korean, Japanese, European	DIHS; SJS-TEN	9.5 (6.4–14)	<0.000001	Warning	30
	HLA-B*1511	Korean	SJS	18.4 (4–88)	0.002	No	33
		Han	SJS-TEN	31 (2.8–350)	0.01	No	36
		Japanese	SJS-TEN	16.3 (4.8–56)	0.0004	No	34

Dapsone	HLA-B*1301	Chinese	DIHS	20.5 (11.6–36.5)	6.8×10^{-25}	No	37
Lamotrigine	HLA-B*38	European	SJS-TEN	6.8 (2–21)	<0.02		38
	HLA-B*1502	Han	SJS-TEN	3.6 (1–11.6)	0.03		39
Methazolamide	HLA-B*5901	Korean	SJS-TEN	250 (13–4814)	<0.001	No	40
Nevirapine	HLA-B*3505	Thai	All	18.9 (4.9–80)	$<1.2 \times 10^{-4}$		41
	HLA-DRB1*0101	Australian	DIHS	4.8 (1.6–14.7)	<0.01		42
	HLA-Cw8	Sardinian	DIHS	14.6 (2.4–88)	<0.05		43
	HLA-C*0401	Malawian	SJS-TEN	5.2 (2.4–11)	0.0002		44
	HLA-Cw*04	Han	DIHS	3.6 (1–11)	0.03		45
Phenytoin	HLA-B*1502	Thai	SJS-TEN	18.5 (1.8–188)	0.005		46
		Han	SJS-TEN	4.3 (2–9.4)	<0.0003	Warning	39
Sulfamethoxazole	HLA-B*38	European	SJS-TEN	8.6 (3.5–21)	<0.003		38

Injection of granulysin into mice leads to clinical findings identical to SJS/TEN.

Additionally, cell surface receptor Fas and Fas ligand (FasL) interaction can trigger KC apoptosis. Activated T cells and NK cells express FasL, however its expression can be induced in KCs. Soluble FasL may be produced by KC in response to T cell derived TNFα and IFN-γ. Blockage of Fas-FasL signaling with intravenous immunoglobulin (IVIg) derived Fas-FasL blocking antibodies has been proposed as a mechanism by which intravenous immunoglobulin (IVIg) works in SJS/TEN, however the role of IVIg in SJS/TEN remains controversial.

As noted above and in Table 1.2, genetic factors, such as HLA-B*1502 in Han Chinese, play an important role in predisposition toward SJS/TEN. Recognition of these pharmacogenetic predispositions has led to the recommendation for pretreatment HLA testing in high-risk populations for abacavir, phenytoin, and carbamazepine. The American College of Rheumatology now recommends HLA testing prior to allopurinol therapy in high-risk populations.

More recent reports suggest that specific T-cell receptor subtypes may also play a role. In an attempt to explain why a small percentage of HLA-B*1502 carriers tolerate carbamazepine, investigators discovered an absence of a specific TCR subtype. Variations in other elements of the immune synapse, such as TCR, could explain lack of/or weaker associations of high-risk subtypes such as HLA-B*1502 and carbamazepine-induced SJS/TEN (Fig. 1.1) in non-Han Chinese.

Variations in individual drug metabolism likely play a role as well. In patients who develop SJS/TEN from sulfa drugs (Fig. 1.2), there is an increased percentage of "slow acetylators" as compared to control populations. While the mechanism is not understood, slow acetylation appears to increase with poorly controlled HIV infection and could contribute to the increased incidence of drug reactions in that population.

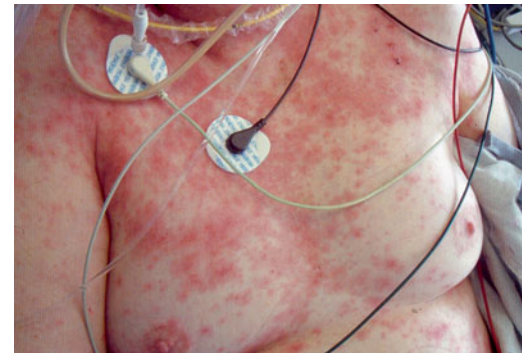

Fig. 1.1 Inflammatory, erythematous, and papular dermatitis over the anterior trunk caused by carbamazepine

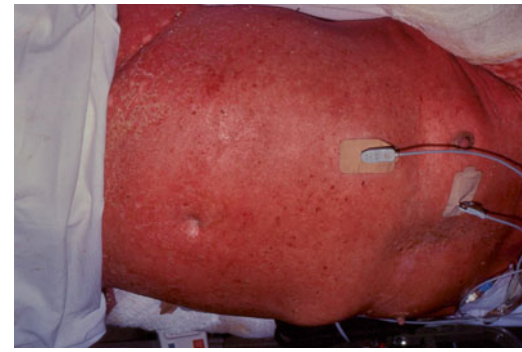

Fig. 1.2 Generalized dermatitis over the trunk with erythema and early erosions caused by sulfamethoxazole

Pustular Drug Reactions

Pustular drug reactions (such as acute generalized exanthematous pustulosis – AGEP) develop due to stimulation of specific immunologic pathways, which lead to neutrophil recruitment and activation (Type IVd). Neutrophil recruitment is regulated by Th17 immune responses via the production of IL-17. IL-17 and IL-22 stimulate KC to express IL-8, which is a strong recruiter for neutrophils. CD4+ T helper and CD8+ cytotoxic T cells are found in cutaneous infiltrates of AGEP. Reports of rapid resolution of AGEP after treatment with TNFα blockers may validate the role of these pathways in development of neutrophilic eruptions. AGEP exhibits clinical similarity to pustular psoriasis. Recently monogenic familial pustular psoriasis was associated with mutations in IL-36 antagonist (IL-36Ra), which lead to increased signaling of the IL-36 pathway once activated. The role of IL-36 in AGEP is under investigation.

Drug-Induced Hypersensitivity Syndrome (DIHS)

DIHS is considered a type IVb hypersensitivity reaction where production of typical Th2 cytokines such as IL-4, IL-13, and IL-5 (increased in early stages of DIHS) and increased expression of IL-5 and eotaxin in lesional skin leads to eosinophil recruitment.

However, the role of the eosinophil in the direct pathogenesis of DIHS is unclear. There are several features which set DIHS apart from other drug reaction syndromes. While most drug eruptions start 1–2 weeks after initiation of therapy, DIHS exhibits a delayed onset (3 weeks to 3 months after initiation of the causative drug). Paradoxical worsening is often noted 3–4 days after withdrawal of the offending drug. Additionally, there is a limited repertoire of drugs associated with the development of DIHS.

Genetic factors also play a role in risk of DIHS. The association of DIHS from the anti-HIV drug abacavir and HLA-B*5701 is well recognized, likely due to changes in the antigen binding groove of HLA-B*5701 resulting from binding of abacavir, leading to altered recognition of self antigens (see above). Similar findings were noted with HLA-B*1502 in cases of DIHS with carbamazepine.

With more detailed study it is becoming clear that there is drug-specific heterogeneity in DIHS. Elevated eosinophils are commonly noted in cases triggered by carbamazepine, but are much less common when abacavir, dapsone, and lamotrigine are the culprits. Allopurinol is often associated with more prolonged disease courses, as well as renal involvement, but other common features of DIHS are rare when it is the causative agent. Thus DIHS is likely a spectrum of individual Type IV (often b) hypersensitivity reactions triggered by specific drugs with some exhibiting overlapping features. The role of viral reactivation in DIHS is discussed below.

Viral Reactivation and Drug Eruptions

The initial detection of human herpes virus 6 (HHV-6) via PCR from blood samples of patients with DIHS in the 2–3 weeks after onset triggered further investigation into the role of viral reactivation in adverse drug reactions.

Mechanisms of Viral/Immune Interaction Leading to Drug Allergy

After clearance of an initial viral infection (for example, HSV) from the skin, there is a small fraction of resident memory T cells that remain to protect peripheral tissue from reexposure to virus. These T_{RM} cells persist for at least 6 months after infection and express CD8, VLA-1, and CD103, which are important for epithelial localization. They are distinct from central memory T cells as they exhibit low expression of CD62L and CD122 but high expression of CD69. They also exhibit a steady state crawling behavior between KC. This migratory dendritic behavior allows detection of antigen expressing target cells in minutes to hours. Skin resident CD8 + T_{RM} cells are long-lived, non-circulating, and better than circulating T_{CM} cells at giving quick long-term protection against skin viral infection. They function to produce a "pathogen alert" for protection against further viral infection or proliferation. The TCR of T_{RM} cells functions almost like a toll-like receptor (TLR) on innate immune cells and T_{RM} cells may act as a bridge between adaptive and innate immune responses.

Recent studies examining the role of T_{RM} cells in fixed drug eruption (FDE) has revealed increased numbers of T_{RM} cells in lesional skin. Recent mouse studies suggest heterologous viral infection of mice leads to a narrow oligoclonal T cell repertoire specific to highly cross-reactive epitopes of different viruses. One current hypothesis suggests that drug antigens recognized by these broadly cross-reactive cells, originally evolved to protect the skin from herpes viruses, triggers their activation, leading to killing of surrounding KC and the formation of the typical FDE. FDE shows similar histologic features to more severe eruptions such as SJS/TEN, which leads to the question of why FDE is limited in scope relative to the more widespread eruptions. Recruitment of FoxP3+ regulatory T