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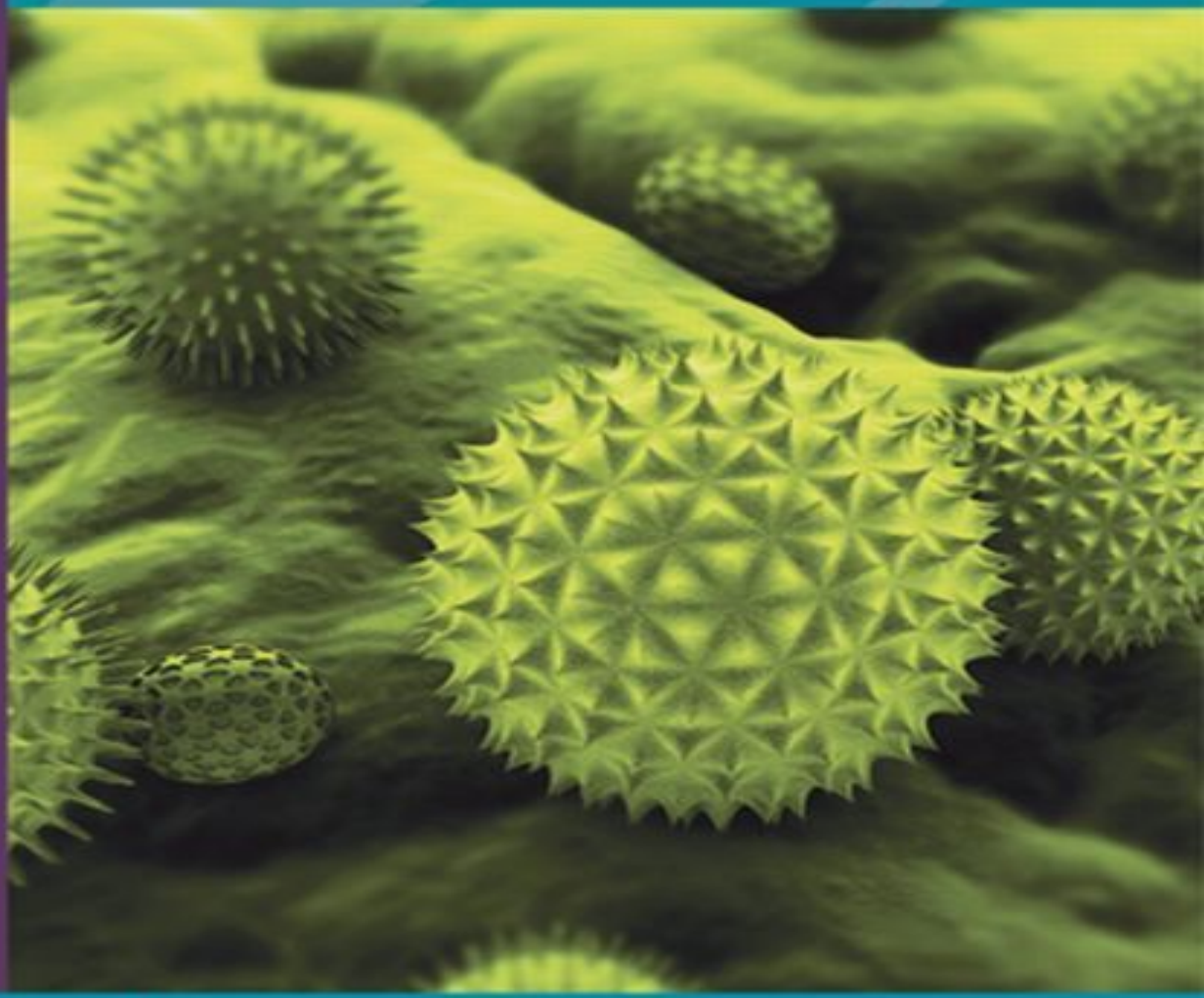
Manual of Allergy and Immunology

FIFTH EDITION

Daniel C. Adelman
Thomas B. Casale
Jonathan Corren



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Fifth Edition

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Editor

Daniel C. Adelman, MD
Adjunct Professor of Medicine
Allergy and Immunology
University of California, San Francisco
San Francisco, California

Thomas B. Casale, MD
Professor of Medicine
Chief, Division of Allergy/Immunology
Department of Medicine
Creighton University
Omaha, Nebraska

Jonathan Corren, MD
Associate Clinical Professor of Medicine
University of California
Director, Research
Allergy Medical Clinic
Los Angeles, California

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To my wife, Deborah, and children, Arielle, Nathan, and Gabriel, for their patience, tolerance, and understanding; and to my parents, Barnet and Beverly, for the years of support and encouragement.

Daniel C. Adelman, MD

To my wife, Jean, my son, Jeffrey, my brother, Bill, and my sister, Mary Ann, for their loving support and encouragement.

Thomas B. Casale, MD

To the memory of my parents, Herman and Mildred Corren, for their inspiration and encouragement, and to my wife, Martha, and children, Jeremy and Rachel, for their loving support.

Jonathan Corren, MD

Contributors

Shradha Agarwal, MD
Assistant Professor
Department of Medicine
Mount Sinai School of Medicine
Assistant Professor
Division of Clinical Immunology
Department of Medicine
Mount Sinai Hospital
New York, New York

Shefalee Admin, MD
Fellow Physician
Pulmonary and Critical Care Medicine
University of California, Los Angeles
Los Angeles, California

Marcella Aquino, MD
Clinical Instructor of Medicine
Department of Internal Medicine
State University of New York at Stony Brook
Stony Brook, New York
Attending, Allergy & Immunology
Department of Internal Medicine
Winthrop University Hospital
Mineola, New York

Robert W. Ausdenmoore, MD
Professor
Department of Pediatrics
Children's Hospital Medical Center
Cincinnati, Ohio

Zuhair K. Ballas, MD
Professor and Director
Division of Immunology
Internal Medicine
University of Iowa Carver College of Medicine
Iowa City, Iowa

Leonard Bielory, MD
Professor
Center for Environmental Prediction
Rutgers University
STARx Allergy & Asthma Center
Springfield, New Jersey
Attending
Medicine, Allergy and Immunology
Robert Wood Johnson University Hospital
New Brunswick, New Jersey

Jack J.H. Bleesing, MD, PhD
Associate Professor
Department of Pediatrics
University of Cincinnati
Attending Physician
Division of Bone Marrow Transplantation
and Immune Deficiency

Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Stephen R. Boden, MD
Fellow
Department of Pediatrics
Division of Allergy and Immunology
Duke University Medical Center
Durham, North Carolina

Mark Boguniewicz, MD
Professor
Department of Pediatrics
University of Colorado School of Medicine
National Jewish Health
Division of Pediatric Allergy-Immunology
Denver, Colorado

Candace Bouler Anz, MD
Fellow, Allergy and Immunology
Section of Pulmonary, Critical Care Allergy and Immunologic Diseases
Department of Internal Medicine
Wake Forest University School of Medicine
Fellow, Allergy and Immunology
Department of Internal Medicine
Wake Forest Baptist Medical Center
Winston-Salem, North Carolina

Lori Broderick, MD, PhD
Allergy and Immunology Fellow
Department of Medicine
University of California, San Diego
La Jolla, California

David Broide, MB, ChB
Professor of Medicine
Department of Medicine
University of California, San Diego
La Jolla, California

Terri F. Brown-Whitehorn, MD
Assistant Professor of Clinical Pediatrics
Department of Pediatrics
Perelman School of Medicine
University of Pennsylvania
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

A. Wesley Burks, MD
Chair
Department Of Pediatrics
University Of North Carolina
Professor
Pediatric Allergy and Immunology
Duke University
Chief
Pediatric Allergy and Immunology
Duke University Medical Center
Durham, North Carolina

Robert K. Bush, MD
Professor Emeritus
Allergy and Clinical Immunology
University of Wisconsin, Madison
Madison, Wisconsin

Jason W. Caldwell, DO
Assistant Professor of Internal Medicine and Pediatrics
Section of Pulmonary, Critical Care Allergy and Immunologic Diseases
Department of Internal Medicine
Wake Forest School of Medicine
Attending Physician
Department of Internal Medicine
Wake Forest Baptist Medical Center
Winston-Salem, North Carolina

Jonathan Corren, MD
Associate Clinical Professor
Department of Medicine
University of California
Director, Research
Allergy Medical Clinic
Los Angeles, California

Charlotte Cunningham-Rundles, MD, PhD
Professor
Department of Medicine and Pediatrics
Mount Sinai School of Medicine
New York, New York

Taylor A. Doherty, MD
Assistant Professor of Medicine
Department of Medicine
University of California, San Diego
La Jolla, California

Mark S. Dykewicz, MD
Professor of Internal Medicine
Director, Allergy and Immunology
Section of Pulmonary, Critical Care Allergy and Immunologic Diseases
Department of Internal Medicine
Center for Human Genomics and Personalized Medicine
Wake Forest University School of Medicine
Director, Allergy and Immunology
Department of Internal Medicine
Wake Forest Baptist Medical Center
Winston-Salem, North Carolina

Nkiruka U. Erekosima, MD, MPH
Assistant Professor
Department of Medicine
Division of Allergy and Clinical Immunology
Johns Hopkins University School of Medicine
Associate Clinical Director

Division of Allergy and Clinical Immunolog
Johns Hopkins University School of Medicine
Baltimore, Maryland

Thomas A. Fleisher, MD
Chief
Department of Laboratory Medicine
National Institutes of Health
Bethesda, Maryland

Luz Fonacier, MD
Professor of Clinical Medicine
Department of Internal Medicine
State University of New York at Stony Brook
Stony Brook, New York
Head of Allergy and Training Program Director
Department of Internal Medicine
Winthrop University Hospital
Mineola, New York

David B.K. Golden, MD
Associate Professor
Department of Medicine
Johns Hopkins University
Director of Allergy Services
Department of Medicine
Sinai Hospital of Baltimore
Baltimore, Maryland

Kernika Gupta, BA
Research Coordinator
Division of Gastroenterology and Nutrition
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Joel M. Hartman, MD
Fellow
Internal Medicine (Allergy/Immunology)
Wake Forest School of Medicine
Wake Forest Baptist Health
Winston-Salem, North Carolina

John M. Kelso, MD
Clinical Professor of Pediatrics and Internal Medicine
University of California, San Diego School of Medicine
Division of Allergy, Asthma and Immunology
Scripps Clinic
San Diego, California

David A. Khan, MD
Professor of Internal Medicine & Pediatrics
Department of Internal Medicine
Division of Allergy & Immunology
University of Texas Southwestern Medical Center
Staff
Department of Internal Medicine

Parkland Memorial Hospital
Dallas Texas

Eric C. Kleerup, MD
Clinical Professor of Medicine
Division of Pulmonary and Critical Care Medicine
David Geffen School of Medicine at UCLA
Los Angeles, California

Stephen C. Lazarus, MD
Professor of Medicine
Division of Pulmonary & Critical Care Medicine
Director, Training Program in Pulmonary & Critical Care
Medicine, Senior Investigator,
Cardiovascular Research Institute
Department of Medicine
University of California, San Francisco
San Francisco, California

Estelle Levetin, PhD
Professor of Biology
Department of Biological Science
The University of Tulsa
Tulsa, Oklahoma

Phil Lieberman, MD
Clinical Professor
Medicine and Pediatrics
University of Tennessee College of Medicine
Memphis, Tennessee

Timothy R. Mainardi, MD, MA
Fellow in Allergy and Immunology
Division of Pulmonary, Allergy and Critical Care
New York Presbyterian Hospital/Columbia University Medical Center
New York City, New York

Mark H. Moss, MD
Associate Professor
Medicine and Pediatrics
University of Wisconsin School of Medicine and Public Health
Attending Physician
Medicine and Pediatrics
University of Wisconsin Hospital and Clinics
Madison, Wisconsin

William A. Neaville, MD
Physician
Dallas, Texas

Harold S. Nelson, MD
Professor of Medicine
Department of Medicine
National Jewish Health
Denver, Colorado

Joao B. Oliveira, MD, PhD

Assistant Chief
Immunology Service
Department of Laboratory Medicine
National Institutes of Health
Bethesda, Maryland

Rodolfo Pascual, MD
Assistant Professor
Department of Internal Medicine
Wake Forest School of Medicine
Attending Physician
Department of Internal Medicine
Wake Forest Baptist Health
Winston-Salem, North Carolina

Debendra Pattanaik, MD
Assistant Professor
Allergy and Immunology
University of Tennessee Health Science Center
Staff Physician
Allergy and Immunology
Veterans Affairs Medical Center
Memphis, Tennessee

Stephen P. Peters, MD, PhD
Professor
Internal Medicine & Center for Genomics
& Personalized Medicine Research
Wake Forest School of Medicine
Attending Physician
Wake Forest Baptist Health
Winston-Salem, North Carolina

Sarbjit S. Saini, MD
Associate Professor
Department of Medicine
Johns Hopkins University
Staff Physician
Department of Medicine
Johns Hopkins Hospital
Baltimore, Maryland

Jessica Savage, MD
Post-doctoral Fellow
Division of Allergy and Clinical Immunology
Johns Hopkins University School of Medicine
Baltimore, Maryland

Jonathan M. Spergel, MD, PhD
Associate Professor
Department of Pediatrics
Perelman School of Medicine at University
of Pennsylvania
Chief
Allergy Section, Division of Allergy and
Immunology
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Jeffrey R. Stokes, MD
Associate Professor
Department of Medicine

Creighton University Medical Center
Allergy/Immunology Program Director
Department of Medicine
Creighton University Medical Center
Omaha, Nebraska

Ricardo A. Tan, MD
California Allergy and Asthma Medical Group Inc.
Los Angeles, California

Ritu Verma, MD
Associate Professor
Department of Pediatrics
Perelman School of Medicine at University of Pennsylvania
Section Chief, Gastroenterology
Division of Gastroenterology and Nutrition
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Robert A. Wood, MD
Professor of Pediatrics and International Health
Division of Allergy and Immunology
Johns Hopkins University School of Medicine
Chief, Division of Pediatric Allergy and Immunology
Johns Hopkins Hospital
Baltimore, Maryland

Michelle R. Zeidler, MD
Assistant Professor of Medicine
Division of Pulmonary and Critical Care Medicine
David Geffen School of Medicine at UCLA
Los Angeles, California

Preface

The fifth edition of the *Manual of Allergy and Immunology* is designed to serve health care professionals in the diagnosis and management of allergic and other immuno-logic disorders. Our goals have been to present the basic and essential material clearly and to provide specific information to assist in clinical decision making and treatment planning.

We selected contributors to this edition for their specific expertise. Only currently accepted therapeutic regimens and dosages are recommended; all material that is considered investigative is so identified. We have attempted to minimize didactic material; what is included has been carefully edited to allow a basic understanding of each subject. More extensive discussions of each subject are referenced in each chapter under Selected Readings. In addition, useful addresses on the World Wide Web have been referenced when such sites are available.

Our overall goal is to have the *Manual* contain the basic information, collected in a single source, that is required for the practice of allergy and clinical immunology. The specialist will find this manual a convenient reference handbook, while the generalist will be able to use the *Manual* as a helpful guide in formulating a diagnostic and therapeutic approach to patients suspected of having an allergic or immunologic disorder. We hope that students, house officers, and other health care professionals will find the *Manual* a useful guide to the clinical practice of allergy and immunology.

Our heartfelt thanks to all of our contributors, for unselfishly giving their time and considerable effort preparing their respective chapters. We also thank Lippincott Williams Wilkins for giving us the opportunity to publish the *Manual*; and our editor Lisa Consoli, for patiently giving encouragement and editorial assistance throughout the preparation of this edition.

Daniel C. Adelman
Thomas B. Casale
Jonathan Corren

Contents

1

Introduction to the Immune System

Lori Broderick, Taylor A. Doherty, and David Broide

I. INTRODUCTION

A. Role of the immune system. The primary role of the immune system is protection of self against continuously evolving pathogens. Normal immune function is characterized by recognition and elimination of microbial pathogens, tumors, and toxins without damage to the host. Imbalances in this complex system can result in either impaired host defense against infections or inappropriate host tissue damage (allergic disease, autoimmunity).

B. Innate and adaptive immune responses. The immune system can be divided into innate and adaptive components. The innate immune system is germline encoded and is evolutionarily more primitive. Activation of innate pattern-recognition receptors (PRRs) leads to rapid production of proinflammatory cytokines and activation of immune cells. Adaptive immunity is characterized by the development of antigen-specific primary and memory responses that occur through random somatic gene rearrangements. Dysfunction of either innate or adaptive responses may have catastrophic effects on the host, including susceptibility to infection (immune deficiency), autoimmunity (loss of self-tolerance), or hypersensitivity.

C. Physical barriers. The host–environment interface is made up of barriers, such as the skin and mucosal surfaces, which contain enzymes and mucus that inhibit the attachment of microbes or are directly antimicrobial. Ciliated surfaces, as are found in the respiratory tract, propel foreign substances out of the host. Additional physiologic barriers that allow the host to be inhospitable for some pathogens include body temperature elevation and low pH as is found in the stomach. Pathogens have evolved distinct mechanisms to overcome these barriers, and additional mechanisms of defense are required for the host to thrive.

II. DEVELOPMENT OF THE IMMUNE SYSTEM

Understanding the development of the immune system provides important insight into mechanisms contributing to B-cell and T-cell immunodeficiencies.

A. Immunity in the fetus and newborn. Human fetal development is a unique state in which a functional immune system develops under potential graft versus host conditions. At 4 to 5 weeks of gestation, the fetal liver acts as the primary site of lymphoid development, and subsequent lymphocyte production occurs in the bone marrow. The third and fourth pharyngeal pouches in the embryo give rise to the thymus, a lymphoid organ, which descends into the mediastinum by 7 weeks of gestation. The thymus is the site of T-cell development and serves as a checkpoint for appropriate T-cell recognition of antigen and prevention of autoreactivity. From 6 to 8 weeks of gestation, large numbers of T-lymphocyte precursors migrate through the thymic layers, with the potential to become circulating immunocompetent T cells. Only about 5% of the developing T cells survive the stringent selection criteria, and those remaining undergo programmed cell death or apoptosis.

The human fetus is able to synthesize IgM antibody by 10.5 weeks of gestation, IgG by 12 weeks, and IgA antibody by 30 weeks. Due to the lack of antigen stimulation *in utero*, the immunocompetent newborn has little circulating IgA and IgM. IgG is nearly completely maternal in origin, delivered by active and selective transport across the placenta. The functional ability of fetal immunoglobulins is limited, with impaired switching to IgG and IgA and failure to respond to certain capsular polysaccharides. Serum levels of immunoglobulins, as well as their function, increase with aging (Table 1-1).

Table 1-1 Immunoglobulin (IgG, IgM, IgA, IgE) Serum Levels in the Fetus and Infant in the First Year of Life

Age	IgG (mg/dL)	IgM (mg/dL)	IgA (mg/dL)	IgE (IU/mL)	Comments
Prenatal	600–1,400	0–4	0	0	Maternal levels of IgG (maternal IgA and IgM do not cross placenta)
Birth	636–1,600	6.3–25	1.4–3.6	0.04–1.28	
2 mo	206–601	17–105	2.8–47		
4 mo	196–558	27–101	4.4–73		Physiologic hypogamma-globulinemia of infancy
6 mo	215–704	35–102	8.1–68	0.44–16.3	
9 mo	217–904	34–126	11–90	0.76–7.31	Complete loss of maternal IgG occurs near 9 mo of age
12 mo	345–1,213 (60% adult level)	43–173 (75% adult level)	14-106 (20% adult level)	0.80–15.2	
Adult	600–1,400	40–345	60–380	1.53–114	

Ranges represent 95% CI. Levels indicated are in mg/dL.

(Modified from Tinkel Vernon HJ. Immunology and allergy. In: Custer JW, Rau RE, eds. Johns Hopkins: The Harriet Lane Handbook, 18th ed. Philadelphia, PA: Elsevier Mosby, 2008.)

There is almost no placental transfer of complement components C1q, C2, C4, C3, and C5, and the total hemolytic complement in the newborn is low. These deficiencies may explain the relative impairment in opsonization found in newborns, as the complement system does not functionally reach an adult level until 3 to 6 months of life. Phagocytic cells are seen in the human fetus at 8 weeks of gestation as myelocytes, and histiocytes are present in the early yolk sac stage of hematopoiesis. Monocytes first appear in the spleen and lymph nodes at 16 to 20 weeks of gestation, with gradual maturation of macrophage function with advanced fetal age.

B. Bone marrow development of B Cells. B cells are generated from mul-tipotent hematopoietic stem cells (HSCs) in the bone marrow before migrating through the circulation to secondary lymphoid organs for further maturation (Fig. 1-1). The commitment to the B-cell lineage is first observed by expression of cell surface markers, such as CD19. The pro–B cells do not express immunoglobulin and undergo gene rearrangement prior to becoming mature B cells (Fig. 1-2). Antigen-inexperienced mature B cells express surface IgM or both IgM and IgD.

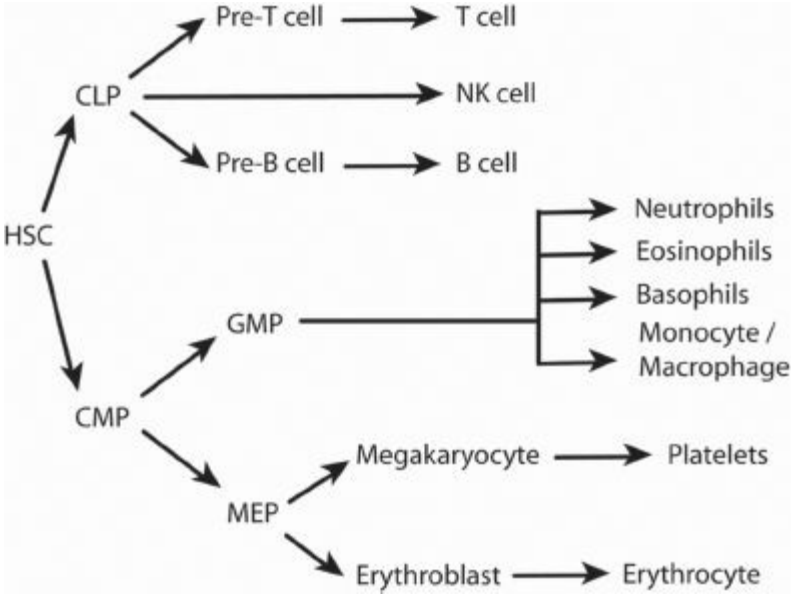

Figure 1-1. Differentiation of hematopoietic stem cells. HSC, hematopoietic stem cell; CLP, common lymphoid progenitor; CMP, common myeloid progenitor; GMP, granulocyte/macrophage progenitor; MEP, megakaryocyte/erythroid progenitor. (Modified from Orkin SH, Zon LI. Hematopoiesis: an evolving paradigm for stem cell biology. *Cell* 2008;132:631–644.)

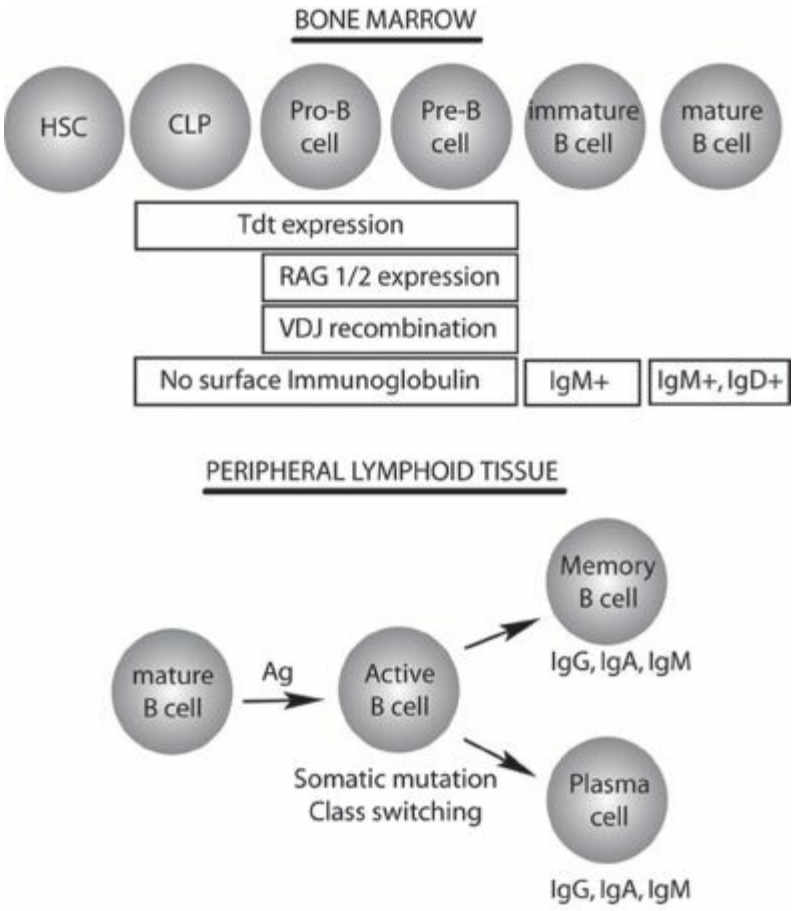

Figure 1-2. B-cell differentiation and development. B cells develop from hematopoietic stem cell precursors in the bone marrow in an antigen-independent process. Maturation of B cells occurs following antigen encounter in peripheral lymphoid organs. The stages of immunoglobulin expression and key enzymes are noted. Ag, antigen; CLP, common lymphocyte progenitor; HSC, hematopoietic stem cell; Ig, immunoglobulin, RAG, recombinase activating gene; Tdt, terminal deoxynucleotidyl transferase.

B cells are able to produce immunoglobulin with exquisite antigen specificity through a process of gene rearrangement. The immunoglobulin molecule has two identical heavy chains and two identical kappa or lambda light chains (Fig. 1-3). The chromosomal light and heavy chain loci are separated into multiple gene segments that code for the variable (V), diversity (D), joining (J), and

constant (C) regions. The rearrangement of these genes is dependent on the lymphoid-specific recombinase activating gene proteins, RAG-1 and RAG-2, and terminal deoxynucleotidyl transferase (TdT). Rearrangement of first the heavy chain and then the light chain leads to assembly of a functional immunoglobulin with specificity for one antigen. The chains are formed by one of many V, D, and J genes recombining along with the addition of nucleotides at the joining ends of each gene cassette, a process known as junctional diversity. Further antibody diversity is created as one unique heavy chain unites with a similarly rearranged unique VJ light chain.

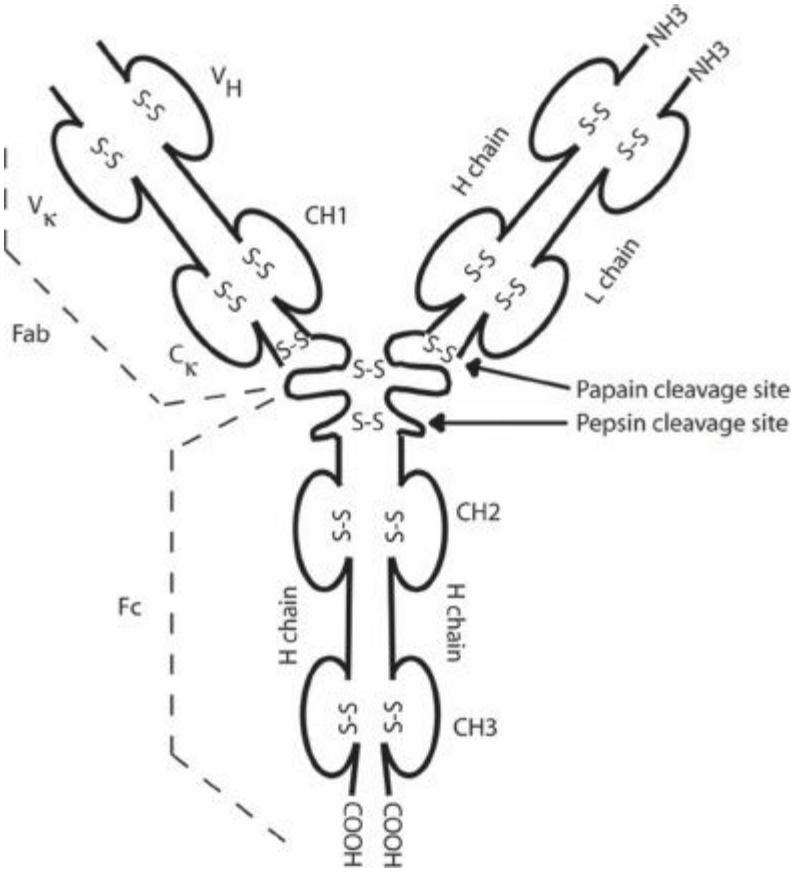

Figure 1-3. Immunoglobulin structure. Basic immunoglobulin structure with immunoglobulin subunits after enzymatic digestion. Interchain disulfide bonds are shown (large S–S), but intrachain bonds have been omitted for clarity. The number of H–H disulfide bonds varies with each class and subgroup of immunoglobulin. Vh and Vk indicate the variable regions of the heavy and light (kappa) chains, respectively; Ch1–3 and Cκ indicate constant regions of the heavy and light (kappa) chains, respectively. H and L indicate heavy and light, respectively. Fab indicates the antigen-binding portion of the antibody molecule; Fc indicates the crystallizable receptor and complement-binding portion of the antibody molecule. (Modified from Kircher S, Marquardt D. Introduction to the Immune System. In: Adelman DC, Casale TB, Corren J, eds. *Manual of Allergy and Immunology*, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2002:1–23.)

Surface immunoglobulin, referred to as the B-cell receptor, has a short cytoplasmic tail that associates with Igα and Igβ and forms a complex that transduces intracellular signals upon antigen binding. The B-cell receptor acts as a survival signal for the cell, and following initial recombination events, the naïve B cell expressing IgM and IgD enters the circulation and migrates to the secondary lymphoid organs. Hypermutation of the immunoglobulin genes takes place following encounter with antigen in the germinal centers of secondary lymphoid organs and leads to a process that increases antigen affinity, called **affinity maturation**. Switching the type of immunoglobulin from IgM to IgA, IgG, or IgE also occurs after antigen exposure and is termed **isotype switching**. B cells that develop into immunoglobulin-secreting plasma cells are either short-lived in tissues or long-lived in bone marrow.

C. Thymic development of T cells. The thymus is the primary site of T-cell development and maturation and is divided into lobules, each with an outer cortex and an inner medulla. Thymocyte progenitors arrive from the bone marrow at the corticomedullary junction and migrate outward to the cortex. The stromal framework of the thymus contains epithelial cells, interdigitating with dendritic cells (DCs) and macrophages that assist in the development of T cells and removal of thymocytes that fail the selection process. The thymus atrophies with age, beginning at puberty, although T-cell development continues throughout life, albeit at a lower volume compared to that in childhood.

During T-cell development, mandatory recognition of foreign proteins in the context of self structures becomes an important checkpoint known as selection (Fig. 1-4). Thymocytes begin as double-negative cells that do not express either CD4 or CD8 and begin the process of recombination to form a T-cell receptor (TCR). The TCR consists of αβ or γδ chains, which are formed by rearranging arrays of variable (V), diversity (D), and joining (J) regions similar to B cells. Rearrangement is dependent on RAG-1, RAG-2, and Artemis, which create the enormous combinatorial and junctional diversity of the T-cell repertoire. Loss of any of these enzymes is associated with a failure to generate T cells and a severe combined immunodeficiency (SCID) phenotype. Large gaps between gene cassettes result in the splicing out of double-stranded DNA that can circularize to form **T-cell receptor excision circles, or TRECs**, which have been introduced as a screening tool for SCID (see Chapter 20, Section VI. A: "Nucleotide-Based Testing"). Successful rearrangement of two TCR genes with surface expression of an αβ or γδ TCR marks the end of the pre–T-cell stage. More than 90% of T cells have rearranged the αβ loci and will become double-positive T cells expressing both CD4 and CD8 and progress through further cell selection and differentiation. However, if the rearrangement of the γδ TCR is successful, the cells remain double negative and emigrate to lymphoid tissues and epithelial tissues.

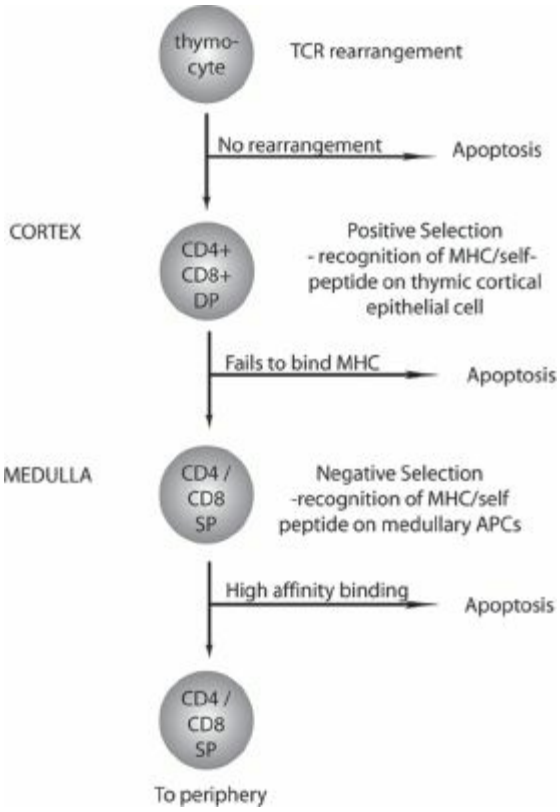

Figure 1-4. Summary of thymic selection. Double-positive thymocytes migrate from the cortex, where positive selection occurs to the medulla for negative selection. Refer to text for further details. APC, antigen-presenting cell; DP, double positive; MHC, major

histocompatibility complex; SP, single positive.

Double-positive T cells in the thymic cortex undergo further selection events to ensure adequate recognition of antigen in the context of self-major histocompatibility complex (MHC) (Fig. 1-4). The T cells initially undergo positive selection in which double-positive T cells interact with self-MHC and self-peptide complexes expressed on cortical thymic epithelium. T cells that do not bind self-MHC undergo apoptosis and are cleared by macrophages. T cells that survive positive selection move to the medulla for negative selection. Negative selection ensures that T cells with high affinity for self-MHC and self-peptide are cleared generating **central tolerance.** The self-peptides expressed by thymic epithelial cells are governed by a gene known as the autoimmune regulator (*AIRE*). Mutations in *AIRE* are responsible for the disease **autoimmune polyendocrinopathy–candidia-sis–ectodermal dystrophy syndrome (APECED)**. During the selection process, double-positive T cells mature to either $CD8^+$ T cells or $CD4^+$ T cells on the basis of their interaction with either MHC class I ($CD8^+$) or MHC class II ($CD4^+$) molecules, respectively. Approximately 30% to 40% of circulating T cells are $CD8^+$ and 60% to 70% are $CD4^+$. Only about 5% of the developing T cells survive the selection events and enter the periphery.

Natural killer T cells (NKT) are another population of T cells that undergo a type of selection process in the thymus but recognize glycolipid presented on MHC-like molecules such as CD1d. NKT cells have an invariant TCR with limited antigen recognition and are largely considered innate cells with the capacity to rapidly produce large amounts of cytokines.

D. Secondary lymphoid tissues. The spleen, lymph nodes, and gut-associated lymphoid tissue (tonsils, adenoids, and Peyer's patches) are secondary lymphoid organs and are organized to facilitate maximal interaction between B and T cells. Lymph nodes are dispersed throughout the body and function to localize the spread of infection. Lymph nodes are arranged in a reticular pattern with a cortex and medulla. B cells are primarily found in the cortex "B zone" (follicles and germinal centers), whereas T cells are primarily found in the "T zone," paracortical cords beneath the follicles. Circulating lymphocytes enter lymph nodes, tonsils, and Peyer's patches from the blood by crossing high endothelial venules. These unique postcapillary venules display adhesion molecules, such as L-selectin, to facilitate the adhesion of lymphocytes and their migration into the lymphoid tissue. The spleen is also divided into T- and B-cell areas similar to that of the lymph node, but circulating lymphocytes enter from the blood through the marginal zone.

III. INNATE IMMUNITY

A. Innate immune cells. The innate immune system is the first line of defense in protecting the host from invading pathogens and toxins. Deficiencies in innate immunity increase susceptibility to infection, while activation of innate inflammatory responses by allergens contribute to enhanced allergic symptoms. Innate immune cells including natural killer (NK) cells, NKT cells, macrophages, DCs, neutrophils, eosinophils, and mast cells contribute to initial inflammatory responses along with structural cells such as epithelial cells.

Natural killer (NK) cells, macrophages, and neutrophils play an important innate immune role in host defense against infections. NK cells are cytotoxic lymphocytes that act as a surveillance cell to

detect viral-infected cells. Activated NK cells rapidly produce large amounts of interferon-gamma (IFN-γ), which inhibits viral replication. NK cells are identified by their expression of CD56 and CD16 and are inhibited by encounter with self-MHC molecules.

Macrophages are phagocytic cells capable of producing a wide range of cytokines, significantly influencing the pro- or anti-inflammatory nature of the immune response. Macrophages are divided into subtypes and include M1 macrophages that promote Th1 responses through interleukin-12 (IL-12) and "alternatively activated" M2 macrophages induced by interleukin-4/ interleukin-13 (IL-4/IL-13) that promote Th2 responses and tissue remodeling. "M2-like" macrophages also exist and are activated by immune complexes.

Dendritic cells (DCs) are innate cells with a critical role in shaping adaptive responses to invading organisms or allergens. DCs play a key role in taking up antigen (or allergen) at mucosal or cutaneous surfaces and transporting the antigen to regional lymph nodes to encounter and expand populations of antigen-specific T cells. There are two general subtypes of DCs: the myeloid DCs and plasmacytoid DCs. **Myeloid DCs** are professional antigen-presenting cells with long-reaching dendritic extensions for sampling antigen and express high levels of CD11c and MHC class II. They are found in tissues and lymphoid structures. **Plasmacytoid DCs** are primarily found in tissues and are characterized by their plasmacytoid morphology. Plasmacytoid DCs express less MHC class II on their surface compared with myeloid DCs, thus limiting their ability to induce T-cell activation. Plasmacytoid DCs have an important role in innate immunity through production of type 1 interferons after toll-like receptor (TLR)-7 and TLR-9 stimulation.

Neutrophils are multilobed granulocytes that contain three classes of granule proteins: primary (azurophil) granules of myeloperoxidase, secondary (specific) granules of lactoferrin, and tertiary (gelatinase) granules of gelatinase. These are formed sequentially during granulocytic differentiation in the bone marrow. Neutrophils make up 50% to 70% of the circulating leukocytes.Upon their emigration from the bone marrow, neutrophils respond to multiple chemokines including IL-8. They have important microbicidal activity, largely through their generation of oxygen radicals. Dysfunction of neutrophils is associated with severe susceptibility to infection, as seen in patients with neutropenia and chronic granulomatous disease (CGD).

Eosinophils are identified by their bilobed nucleus and specific granules. The Th2 cytokine IL-5 stimulates eosinophil development from $CD34^+$ hematopoietic progenitor cells in the bone marrow. They represent 1% to 6% of leukocytes in circulation and migrate to sites of inflammation in response to eotaxin-1 and RANTES. Their survival depends on continued exposure to IL-5, as well as granulocyte macrophage colony–stimulating factor (GM-CSF), and IL-3. Eosinophils are effector cells in allergic responses and are important in antiparasitic inflammatory responses, in part through mediators such as major basic protein.

Mast cells are tissue resident cells derived from bone marrow progenitor cells. They play a key role in IgE-mediated immediate hypersensitivity reactions but can also be activated by non-IgE-mediated pathways. Two subsets of mast cells have been identified based on the contents of their secretory granules. **Connective tissue–type mast cells (MCTC)** are found in the skin, and their granules contain tryptase and chymase, whereas **mucosal-type mast cells (MCT)** contain tryptase but not chymase. Mast cells have surface IgE bound to the high-affinity IgE receptor (FcεR1). Antigen binding to surface IgE results in cross-linking and release of preformed mediators such as histamine, as well as synthesis of leukotrienes and a variety of cytokines including TNF-α, IL-3, IL-4, IL-5, IL-8,

IL-10, IL-13, and MCP-1.

Basophils are granulocytes characterized by a lobulated nucleus and basophilic cytoplasmic granules containing histamine. Basophils represent <3% of leukocytes in the circulation and, like mast cells, have high-affinity receptors for IgE (FcεRI). They contribute to immediate and late-phase allergic reactions and are capable of generating cytokines including IL-4, IL-13, TSLP (see Section III D), and IL-25.

B. Phagocytosis. Phagocytosis is the process of engulfment of material by cells. Immune cells capable of phagocytosis include the circulating granu-locytes (neutrophils and monocytes) and the cells of the reticuloendothelial system including liver Kupffer cells, splenic macrophages, pulmonary alveolar macrophages, and CNS microglial cells. Phagocytic cells are responsible for removal of microorganisms as well as apoptotic cells. Migration occurs through chemotaxis toward activated complement components (C3a, C4a, C5a), bacterial products, leukotrienes, and other mediators. Extracellular substances are recognized and internalized into a specific organelle known as a **phagosome**. The phagosome permits isolation and localization of the pathogenic material into an intracellular vacuole, separate from host cell functions, where metabolic activation can destroy the foreign material. NADPH oxidase generates superoxide anion radicals that are microbicidal and lead to an oxidative burst within the phagosome. Mutations in NADPH oxidase are responsible for **chronic granulomatous disease** (see Chapter 18, "Primary Immunodeficiency Diseases"), in which a defective oxidative burst leads to reduced pathogen killing by neutrophils and immunodeficiency.

C. Pattern-recognition receptors. PRRs are germline-encoded, innate danger signal sensors that detect invariant pathogen pattern motifs and initiate an inflammatory response appropriate to the type of pathogen threat encountered. Diseases linked to PRRs include immunodeficiencies, inflammatory bowel disease, and hereditary autoinflammatory syndromes. There are two broad categories of recognized patterns, **pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs).** PAMPs are microbial in origin, and DAMPs are nonmicrobial danger signals such as the presence of intracellular uric acid crystals in gouty arthritis. Recognition of both PAMPs and DAMPs by PRRs provide for the detection and response to a wide variety of "danger" signals. Four distinct subsets of PRRs have been identified, including TLRs, C-type lectin receptors (CLRs), nucleotide-binding oligomerization domain (NOD), leucine-rich repeat containing receptors (NLRs), and retinoic acid–inducible gene I protein (RIG-I) helicase receptors.

There are 13 mammalian TLRs, 10 of which have been identified in humans and are designated by extracellular domains containing leucine-rich repeats and cytoplasmic Toll/IL-1R homology (TIR) domains required to initiate signaling. TLRs act by forming homo- or heterodimers with other TLR family members, or heterodimers with other PRRs. TLRs are highly expressed on DCs, macrophages, and neutrophils and recognize bacteria, viruses, and fungi. For example, TLR4 recognizes LPS in the gram-negative bacterial cell wall, and TLR9 recognizes CpG motifs present in bacterial DNA. TLRs 1, 2, 4, 5, and 6 are located mainly on the cell surface, whereas TLRs 3, 7, 8, and 9 are found in endocytic compartments. TLR signaling molecules include interleukin-1 receptor–associated kinase 4 (IRAK4) deficiency and myeloid differentiation primary response gene 88 (MyD88). Deficiency of IRAK5 and MyD88 has recently been discovered as a cause of rare primary immunodeficiencies.

CLRs are primarily membrane-bound and include dectin-1, dectin-2, macrophage mannose

receptor, and the circulating protein mannose-binding lectin (MBL). They are expressed on macrophages, DCs, and neutrophils and are essential for recognition of fungi and bacteria. RIG-1 helicase receptors are cytoplasmic PRRs that sense viral nucleic acids. RIG-helicase members RIG-1 and MDA5 recognize dsRNA. The NLRs (NOD1 and NOD2) are cytoplasmic PRRs that recognize peptidoglycans of bacterial cell wall, and mutations in the NOD2 gene are associated with development of inflammatory bowel disease. The NLR member NLRP3/cryopyrin forms a multimeric complex known as the "inflammasome" that activates processing of proinflammatory cytokines IL-1β and IL-18. Mutations in NLRP3 are responsible for cryopyrin-associated periodic syndromes, a group of hereditary inflammatory diseases that variably affect the skin, joints, and central nervous system.

D. Innate allergic responses. An important role of innate immunity in allergic responses has become increasingly evident. Innate immune cells such as macrophages, DCs, eosinophils, mast cells, basophils, and structural cells such as epithelial cells are implicated in initiating and possibly propagating the allergic response. Bronchial epithelial cell contact with allergens leads to the upregu-lation of neutrophil and eosinophil chemoattractants including eotaxin and RANTES. Additionally, the epithelium produces thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 that have important roles in shaping the adaptive Th2 immune response. TSLP induces DCs to express the costimulatory TNF family member OX40 ligand that drives differentiation of naïve T cells into Th2 cells. Macrophages can be activated by allergens to produce a wide variety of inflammatory mediators, and M2 macrophages produce chemokines for Th2 cells, eosinophils, and basophils.

Several other innate cell types have been identified recently, which appear to play a role in initiating allergic responses including natural helper cells and NKT. Natural helper cells do not express classic hematopoietic lineage markers and have been shown to produce high levels of IL-5 and IL-13 in response to IL-25 and/or IL-33. NKT cells have been shown to produce IL-4 and IL-13 upon stimulation and can be activated by IL-25 and IL-33. The combined cytokine and cellular milieu during the innate response to allergens skews toward a Th2 response. This is propagated by local DCs through maintenance of $CD4^+$ T cells at the site of inflammation, further expansion of allergen-specific $CD4^+$ cells, and memory T-cell generation.

E. Complement. The complement system contains more than 30 plasma and cell-membrane proteins that form three enzymatic cascades: the classical pathway, the alternative pathway, and the MBL pathway (Fig. 1-5). Diseases associated with abnormalities of the complement cascade include hereditary angioedema (HAE) and immunodeficiencies. The **classical pathway** is initiated by antibody–antigen immune complexes and apoptotic cells. Binding of these initiators to C1q leads to subsequent binding of C1r and C1s with activation of C4 and C2. The C3 convertase C4b2a is formed by activated C2 and C4 and is the central protease in the pathway. The **alternative pathway** is initiated by the hydroxyl group of microbes binding to C3b. C3b binds factor B, leading to activation of factor D and the formation of a C3 convertase complex, C3bBb. The **mannose-binding lectin (MBL)** pathway is initiated by the binding of terminal mannose groups of microorganisms to MBL and MBL-associated serine proteases 1 and 2 (MASP-1 and MASP-2). This complex is similar to the activated C1 of the classical pathway and subsequently forms C3 convertase through activation of C4 and C2. The integration of the complement pathways is summarized in Figure 1-5.

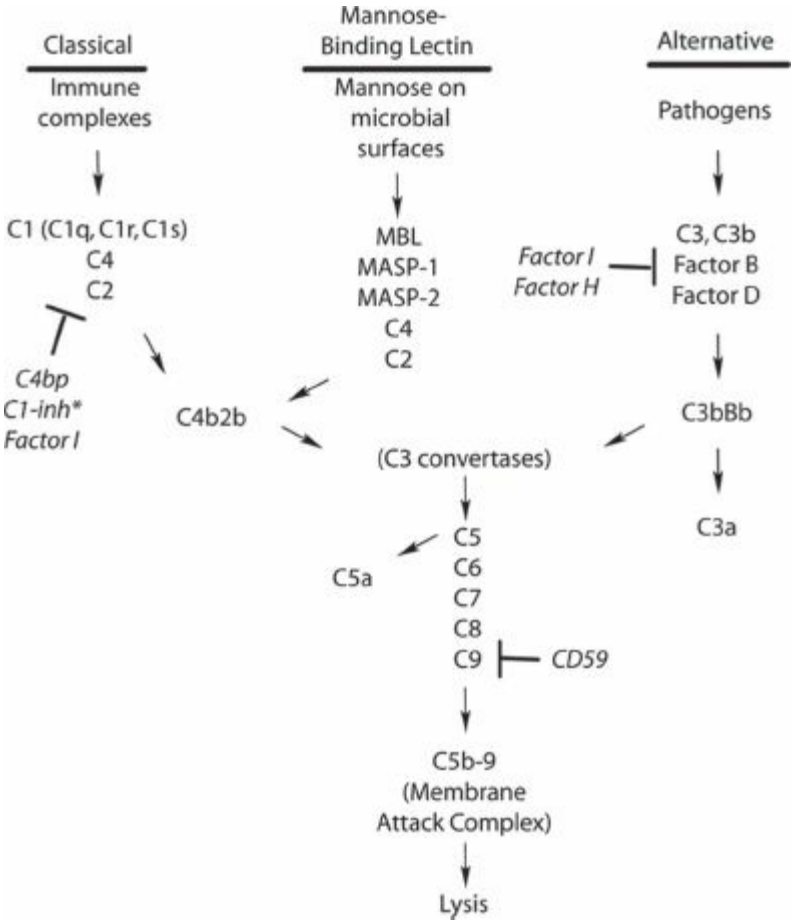

Figure 1-5. Integration of complement pathways. *C1-inhibitor (C1-inh) is critical in suppression of other pathways as well, including the contact activation. C1-inhibitor deficiency or dysfunction leads to consumption of C4 and C2 in the complement pathway and increased production of bradykinin in the contact system (not shown). C1-inhibitor MBL, mannose-binding lectin; MASP-1, MBL-associated serine protease 1; MASP-2, MBL-associated serine protease 2.

In each of these pathways, the formation of a **C3 convertase** is the critical step. C3 is cleaved by C4b2a in the classic pathway and C3bBb in the alternative pathway. Cleavage of C3 leads to generation of C3a (an anaphylatoxin along with C5a) and C3b. C3b deposition on the cell surface increases opsonization as well as formation of the **membrane attack complex** (MAC). The MAC is a self-assembly complex of serum proteins C5b, C6, C7, C8, and C9 that forms a pore in the membrane of the target cell leading to osmotic lysis. A deficiency in any of these proteins is detrimental to the host by increasing susceptibility to infection, specifically neisserial infection (C3 or MAC component deficiency) or pyogenic bacterial infection (C3 deficiency), or increasing susceptibility to autoimmune-mediated disease through failure to clear antibody–antigen complexes (C1, C4, or C2 deficiency).

Several inhibitors of the complement pathway exist to control local inflammation and prevent damage to host cells by inhibiting assembly of either the C3-cleaving enzymes or inhibiting formation of the MAC. These regulators include the soluble proteins factor H, factor I, C1-inhibitor, and C4 binding protein and the membrane-bound CR1, membrane cofactor protein (MCP, CD46), decay accelerating factor (DAF, CD55), and CD59. A deficiency in one of these regulators may lead to increased C3 activation and MAC formation. C1-inhibitor (C1-inh) is a regulator of the complement system, the contact system, and the intrinsic coagulation pathway via the inactivation of plasma kallikrein and of coagulation factors XIa and XIIa protein. C1-inh deficiency or dysfunction, and subsequent upregulation of bradykinin, is implicated in the pathogenesis of HAE, characterized by recurrent episodes of severe angioedema of the face, extremities, GI tract, and larynx.

IV. ADAPTIVE IMMUNITY

An important distinguishing feature of the adaptive immune response is the ability to form immunologic memory. B and T cells are the primary cell types involved in adaptive immunity. These cells originate in the bone marrow and comprise approximately 40% of the total number of white blood cells in the circulation (10% to 15% B cells and 70% to 80% T cells). Along with other immune cells, B and T cells are identified by surface marker expression known as the cluster of differentiation (CD) designation. T lymphocytes express CD3 and are further divided into CD4- and CD8-positive cells. B markers include CD19, CD20, and B220. In contrast to other lymphocytes such as NK cells, B- and T-cell progenitors undergo multiple recombination events leading to receptor specificity and diversity that are critical for their role as effector cells of the adaptive immune system.

A. Humoral immunity

1. **B cells**. B cells are characterized by their ability to produce immunoglobulins and are broadly divided into B1 and B2 subsets. B1 cells are polyreactive and have relatively low antigen-binding affinity, whereas B2 cells are reactive to specific antigen epitopes with high affinity. B1 cells are mainly found in the pleural and peritoneal cavities of adults and express high levels of CD5.

   The differentiation from naïve B cells to memory cells and plasma cells capable of producing high-affinity antibody, even years after initial antigen encounter, is the hallmark of the humoral immune system. Antigen-specific activation of B cells occurs following the binding of antigen to membrane-bound immunoglobulin. Under the influences of a variety of cytokines, B cells undergo clonal expansion. Much of the expanding population become immunoglobulin-secreting plasma cells, while some cells persist as memory B cells defined by the marker CD27. Four to five days after antigen exposure, high titers of IgM can be detected in the circulation and between 10 and 14 days IgG antibodies become detectable. Antibody titers slowly decline over months to years, but small subsets of memory B cells generated during the initial antigen encounter rapidly expand after reexposure to the same antigen. This memory response is more rapid and robust than the primary response, and IgG tends to be the dominant immunoglobulin produced.

2. **Immunoglobulins.** Immunoglobulins are the primary functional arm of the humoral immune system through their ability to bind and neutralize pathogens as well as activate complement and antibody-dependent cell-mediated cytotoxicity. The structure and diversity of these proteins provides critical protection from pathogens and toxins.

   a. Structure. Immunoglobulins are composed of two light and two heavy glycosylated polypeptide chains, linked by disulfide bonds that form a symmetric immunoglobulin molecule with two identical antigen-binding sites (Fig. 1-3). The amino terminus of each chain possesses a variable domain, which differs between antibody molecules. This variable region contains three subregions known as hypervariable complementarity-determining regions (CDRs) and is the site of antigen binding. The carboxy terminus of both the heavy and light chains forms the constant regions and further defines the class and subclass of the antibody. This region also determines which of the two light chains (kappa or lambda) the antibody contains.

Immunoglobulins are further divided into five distinct classes, or isotypes, based on the structure of their heavy chain, specifically, IgA, IgG, IgM, IgD, and IgE (Table 1-2). Each immunoglobulin molecule has only one class of light chain and only one class of heavy chain. Additionally, there are two subclasses of IgA (IgA1 and IgA2) and four subclasses of IgG (IgG1 to IgG4). The carbohydrate portion of immunoglobulin comprises 3% to 13% of the molecule and aids in maintaining the structure of the immunoglobulin.

Table 1-2 Characteristic Features of the Five Classes of Immunoglobulins

Immunoglobulin	Heavy Chains	Light Chains	Molecular Weight (Daltons)	Serum Concentration (mg/dL)	Present in Secretions	Presence of Additional Molecules	Serum half-Life (Days)	Placental Transfer	Classic Complement Activation	Alternate Complement Activation	Biologic Activity (function)
IgG	Gamma (γ_1) (γ_2) (γ_3) (γ_4)	Kappa or lambda	150,000	600–1,400 (280–800) (115–570) (24–120) (5–125)	–	–	23	+ + + + +	+ + + + –	–	Neutralization, opsonization, bacteriolysis, agglutination, hemolysis; IgG1 is the most abundant antibody in serum
IgM	Mu (μ)	Kappa or lambda	900,000	40–345	±	J chain	5	–	+	–	Receptor on B cell, first detectable antibody in humoral immune response, neutralization, hemolysis, agglutination, bacteriolysis, opsonization
IgA	Alpha (α_1) (α_2)	Kappa or lambda	160,000 (secretory IgA, 370,000)	60–380	+	J chain and secretory component for secretory IgA	6			+	Neutralization, present in secretions
IgD	Delta (δ)	Kappa or lambda	180,000	0.3–3	–	–	3	–	–	+	Receptor on B cell
IgE	Epsilon (ε)	Kappa or lambda	200,000	1–114	±	–	2	–	–	+	Mast cell binding, basophil binding, and increased vascular permeability on antigen exposure

Ig, immunoglobulin; +, present; -, absent; ±, possibly present.

(Modified from Kircher S, Marquardt D. Introduction to the immune system. In: Adelman DC, Casale TB, Corren J, eds. Manual of Allergy and Immunology, 4th ed. Philadelphia, PA: L ippincott Williams & Wilkins, 2002:1–23.)

Antibody can exist either as a circulating molecule or as a membrane-bound molecule on the B-cell surface functioning as the B-cell receptor. The membrane-bound form has a hydrophobic trans-membrane portion that functions as an anchor. Monomeric antibodies, such as IgG and IgE, are single immunoglobulin molecules. IgM forms pentamers that allow for more proficient agglutination and sequestration of antigen. To stabilize multimeric forms, the joining chain (or J chain), also produced by B cells, is attached to the immunoglobulin molecule by a disulfide bond. IgA can form dimers and is the primary immunoglobulin found in mucosal surfaces. An additional molecule is incorporated to secretory IgA, known as the **secretory component**, to protect the molecule from proteases in mucosal surfaces such as the GI tract.

b. Diversity and class switching. The antigen specificity of an antibody molecule depends upon the amino acid sequences in the antigen-binding portions of the heavy and light chain variable domains. Although the information needed for an immunoglobulin molecule to be produced is coded for in the DNA, the ability of B cells to rearrange multiple gene segments allows for the generation of virtually unlimited antibody diversity from a relatively small pool of chromosomal DNA. Subsequent hypermutation further diversifies the B cell population.

Isotype switching refers to changing class of antibody, usually from IgM to either IgG, IgA, or IgE. During T-cell–dependent B-cell immune responses, somatic mutation and isotype switching occur within the germinal centers of secondary lymphoid tissues. When the immature B-cell receptor (IgM^+) binds antigen, the cell upregulates expression of the costimulatory molecules CD80 and CD86. Subsequently, B cells interact with antigen-specific $CD4^+$ T cells in the germinal center, leading to maturation of the B cell through somatic mutation and isotype switching. **Somatic mutation** is the process by which the fully recombined VDJ (heavy chain) and VJ (light chain) genes undergo point mutations, which can alter the specificity or the affinity of the antibody for the antigen. **Isotype switching**, the determination of whether a cell will produce antigen-specific IgG, IgA, or IgE, is dependent on the interaction of T-cell CD40 ligand (CD40L) with B-cell CD40 and specific cytokines. Defects in CD40 or CD40L lead to class switch impairment and are responsible for the immune deficiency hyper-IgM syndrome. The processes of isotype switching and somatic mutation are coincident with the development of plasma cells and B-cell memory, permitting rapid induction of high-affinity antibody production upon reexposure to antigen.

T-cell–independent B-cell responses occur in response to polymeric antigens, likely due to cross-linking of multiple immunoglobulin molecules on the B-cell surface. However, the lack of T-cell help results in a failure of somatic mutation to occur, and responses to these antigens remain relatively weak compared with T-dependent B-cell responses.

3. Immunoglobulin isotypes. Immunoglobulins are divided into five major isotypes, described below. The characteristic features of the immunoglobulin isotypes and subclasses are summarized in Table 1-1.

a. Immunoglobulin M (IgM) is the first antibody expressed during B-cell differentiation. The monomeric form has low affinity, but B-cell maturation leads to secretion of multimeric IgM. The IgM pentamer consists of five subunits that are linked by disulfide bonds and J chains. IgM is not transferred across the placenta. The early expression of IgM has led to its use in the diagnosis of recent exposure to pathogens as IgM-expressing B cells respond quickly to antigens. Furthermore, pentameric IgM readily opsonizes microbes and fixes complement, leading to the efficient destruction of extracellular pathogens.

b. Immunoglobulin D (IgD) is present at very low levels in the serum due to high sensitivity to proteolysis. Although its structure is similar to that of the other immunoglobulins, its functional role in either secreted or membrane-bound forms is still not well understood. Notably, there is a rare periodic fever syndrome termed hyper-IgD syndrome (HIDS) characterized by recurrent fevers along with inflammation of the skin, eyes, joints, and GI tract. Although serum IgD is elevated in these patients, it does not appear to be directly involved in the pathogenesis.

c. Immunoglobulin A (IgA) is the predominant immunoglobulin in mucosal secretions of the respiratory, gastrointestinal, and genitourinary tracts and is the second most prevalent in serum after IgG. IgA is found at high concentrations in human colostrum and breast milk. TGF-β is an important switch factor for IgA production. There are two subclasses of IgA1 and IgA2, which differ primarily in the structure of their hinge regions. Serum IgA is primarily monomeric, and more than 90% is IgA1, while secretory IgA is primarily IgA2

and exists as dimers. The secretory chain, which serves to transport IgA into secretions, allows IgA to protect the host from pathogens at the mucosal level. Interestingly, secretory IgA is a particularly potent inducer of eosinophil degranulation. Selective IgA deficiency is the most common primary immunodeficiency in humans, affecting between 1 in 400 and 1 in 700 individuals, with the majority being asymptomatic.

d. **Immunoglobulin E (IgE)** is normally present at the low serum concentrations but is elevated in individuals with allergic disease, hyper-sensitivity reactions, as well as parasitic infestations. Class switching to IgE is induced by IL-4 and IL-13 via activation of the STAT6 pathway. IgE binds with high affinity to FcεRI expressed on mast cells, basophils, and Langerhans' cells and can persist for months. Cross-linking by allergen of two IgE molecules affixed to FcεRI on mast cells or basophils results in the release of inflammatory mediators involved in the immediate hypersensitivity response.

e. **Immunoglobulin G (IgG)** is the most prevalent antibody in human serum and has the longest half-life of the immunoglobulin isotypes. IgG antibodies have high affinity and are associated with secondary immune responses.

IgG is further divided into four subclasses, IgG1, IgG2, IgG3, and IgG4, based on structural differences in the constant region of the heavy chain. They were initially numbered by their prevalence in the peripheral blood. The subclasses differ in the ability to fix complement, antigen target type (protein vs. polysaccharide), and the cytokines that induce isotype switching. **IgG1** is the most abundant of the subclasses and is the primary subclass responsible for immunity to tetanus/diphtheria and has a role in the primary immune response against viral respiratory agents. **IgG2** is generally induced in response to poly-saccharide antigens, such as pneumococcal and meningococcal bacteria. The Th1 cytokine IFN-γ induces class switching to IgG2. **IgG3** fixes complement most efficiently and, along with IgG1, is involved in the primary immune response against viral respiratory agents. In addition, IgG3 appears to be the primary subclass involved in the antibody response against *Moraxella catarrhalis*. **IgG4** is also associated with polysaccharide antigens and is the only IgG subclass that does not fix complement. Notably, IgG4 increases after allergen immunotherapy. The clinical significance of IgG subclass deficiency remains somewhat controversial, but studies suggest that patients with specific subclass deficiency may be more likely to develop infections of the respiratory tract. IgG2 deficiency is the most commonly described subclass deficiency in children, and IgG3 is the most common subclass deficiency in adults. IgG2 and IgG4 are decreased in some IgA-deficient individuals, which may be the reason these patients have more infections.

4. **Immunoglobulin function.** The function of immunoglobulin is to protect the host from invading pathogens through antigen recognition, opsonization, and activation of complement and antibody-dependent cell-mediated cytotoxicity (ADCC). Enzymes such as papain and pepsin cleave the immunoglobulin molecule into two distinct functioning components, Fab and Fc fragments (Fig. 1-3). Papain cleaves the molecule into two identical Fab fragments and one Fc fragment, and pepsin breaks the molecule into a single $F(ab')_2$ fragment and multiple Fc fragments. The Fab end of an immunoglobulin molecule consists of the amino terminus of both heavy and light chains and is the antigen-binding region due to the presence of hypervariable portions. The Fc end of the immunoglobulin

molecule consists of the carboxyl terminal portions of the heavy chains. The Fc portion is not involved in antigen recognition but functions in the rate of synthesis and breakdown of the antibody. Further, the effector functions of the immunoglobulin reside in the Fc binding to Fc receptors on many cell types including macrophages, platelets, granulocytes, and mast cells, leading to subsequent activation of the complement system or ADCC.

5. **Role of IgE in allergy.** Activation of allergen-specific T cells leads to the production of Th2 cytokines including IL-4, which induces B cells to class switch to IgE. IgE antibodies bind the high-affinity IgE receptor FcεRI expressed on mast cells and basophils. Cross-linking of the FcεRI leads to the release of preformed mediators (e.g., his-tamine, tryptase), newly synthesized lipid mediators (e.g., PGD2, LTC4), and transcribed cytokines that promote the allergic response. In the allergic patient, increased quantities of circulating IgE lead to increased expression of FcεRI on mast cells and basophils, which, in turn, enhances the IgE-mediated effector response. The basis of allergy skin testing is to detect the wheal-and-flare response in the skin from histamine release after allergen binds specific IgE affixed to cutaneous mast cells. Anti-IgE therapy is used in asthma, as it reduces FcεRI expression on mast cells and basophils and inhibits the Fc portion of IgE from binding FcεRI.

B. Cell-Mediated Immunity

1. **Antigen recognition. DCs** that have captured antigen migrate to local lymphoid tissue and present antigen to T cells present in the secondary lymphoid organs. T cells with antigen specificity for the presented antigen peptide are activated if costimulation "second" signals are present and undergo clonal expansion by approximately 1,000-fold. The activated T cells acquire effector function, frequently with enhanced expression of multiple cytokines, and home to areas of inflammation. In the tissues, the T cells stimulate many cell types through cytokine production and cell–cell contact. Importantly, after the antigen is cleared, contraction of the expanded T-cell population occurs as most effector T cells die. The few memory T cells remaining are able to mount a rapid immune response if the antigen is again encountered. Of note, T-cell activation can also occur after circulating soluble antigen is trapped in lymphoid organs or tissues and presented.
2. **MHC and antigen processing.** T cells only recognize antigen in the context of the specific self-glycoprotein **major histocompatibility complex (MHC)**. This precise recognition system is known as MHC restriction. There are two subsets of MHC molecules: MHC class I that binds peptide fragments synthesized within the cell and MHC class II that binds peptides that have been ingested and processed by the presenting cell. T cells that are CD8 positive recognize antigen peptide in the context of MHC class I, and CD4-positive cells recognize antigen bound to class II.

In humans, HLA-A, HLA-B, and HLA-C are the three major classes of MHC class I molecules (or histocompatibility leukocyte antigens) and are located on chromosome 6. The class I genes code for the α- polypeptide chain, and the β2-microglobulin gene, on chromosome 15, encodes for the β-chain of the class I molecule. The α-chain has four domains: two peptide-binding domains (α1 and α2), one immunoglob-ulin-like domain (α3), and a cytoplasmic tail. The TCR interacts with both the peptide and the flanking α domains. The α3 domain interacts with the CD8 molecule on $CD8^+$ T cells, stabilizing the

interaction of the T cell and the antigen-presenting cell.

Class I genes are expressed on all nucleated cells of the body. **Peptides binding HLA class I molecules are endogenous antigens** derived from proteins synthesized in the host cell. These proteins are ubiquitinated and degraded into peptide fragments by a proteasome. The peptides produced are of the appropriate length and charge for binding the MHC class I molecule and are transported to the endoplasmic reticulum and loaded into the class I protein-binding groove. The class I molecule with peptide can then interact with β2 microglobulin, stabilizing the entire molecule for transport through the Golgi complex and ultimately to the cell surface. This pathway is critical for presenting viral peptides from an infected cell as well as tumor antigens. Under unique circumstances, exogenous antigens that would normally be presented on MHC class II are internalized, processed, and presented in MHC class I molecules. This phenomenon is known as cross-presentation.

Three major classes of MHC class II proteins are HLA-DR, HLA-DQ, and HLA-DP. They are also located on chromosome 6 and code for the class II α and β polypeptide chains. Each of the class II α and II β chains has four domains: the peptide-binding domain (α1 or β1), the immunoglobulin-like domain (α2 or β2), the transmembrane region, and the cytoplasmic tail. The β2 domain interacts with the CD4 molecule on $CD4^+$ T cells, similarly stabilizing the T cell–antigen-presenting cell interaction.

HLA class II genes are expressed constitutively by antigen-presenting cells, including B cells, DCs, and macrophages, and can be induced by cytokines such as IFN-γ. **Peptides binding HLA class II molecules are exogenous antigens**, which are taken up by endocytosis or phagocytosis. The resulting vesicles join with lysosomes or endosomes that contain proteolytic enzymes in an acidic microenvironment, leading to degradation of the antigen into linear peptide fragments. The peptide fragments join HLA class II molecules in the MHC II loading compartment and are transported back to the cell surface.

3. **T cell phenotypes and cytokine production.** The identification of effector T helper cell subsets characterized by their production of distinct cytokine profiles has provided significant insight into pathogenic adaptive immune responses. The differentiation of naïve T cells into specific "Th" lineage cells is dependent on the cytokine milieu and other factors such as type of costimulation or second signals. Table 1-3 summarizes the actions of many cytokines that regulate or are produced in T-cell–mediated inflammation. Each Th cell subset orchestrates adaptive immune responses by secreting a set of cytokines that regulate immune and stromal cell function (Fig. 1-6). Novel Th lineages continue to be discovered, but the well-characterized lineages are Th1, Th2, and Th17. Recently, Th9 and Th22 cells have been described, and continued work will further characterize these lineages. Recent evidence also points toward significant overlap in cytokine profiles produced by different Th lineages as well as the presence of significant lineage plasticity.

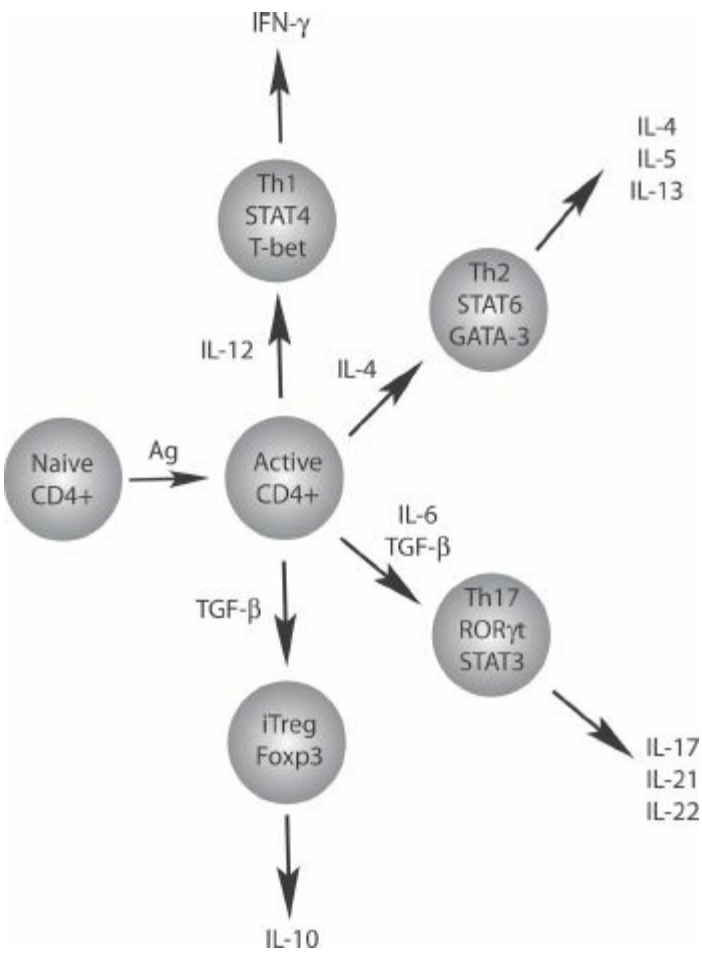

Figure 1-6. Differentiation of T-cell subsets. Multiple $CD4^+$ T-cell subsets are differentiated depending on the cytokine milieu. Lineage-specific transcription factors govern Th differentiation from naïve $CD4^+$ T cells and their production of cytokines. Th1 cells are activated by IL-12 and express the transcription factors T-bet/STAT4, leading to IFN-γ production. Th2 cells are induced by IL-4, upregulating the transcription factors GATA-3 and STAT6 for production of IL-4, IL-5, and IL-13. Th17 cells are induced primarily by IL-6 and TGF-β with RORγt and STAT3 regulating production of IL-17 and IL-22. Induced Tregs in the periphery are generated by TGF-β to express the transcription factors FoxP3 and STAT5, leading to IL-10 and TGF-β production. Ag, antigen; IL, interleukin; TGF, transforming growth factor; TNF, tumor necrosis factor. (Modified from Annunziato F, Romagnani S. Heterogeneity of human effector $CD4^+$ T cells. *Arthritis Res Ther* 2009;11:257.)

Table 1-3 Selected Cytokines and Their Major Sources and Activities

Cytokine	Primary Sources	Primary Effects
Granulocyte colony-stimulating factor (G-CSF)	Monocytes, fibroblasts, epithelial cells	Maturation and differentiation of granulocytes
Granulocyte macrophage colony-stimulating factor (GM-CSF)	Activated macrophages and T cells	Proliferation, differentiation, activation, and prolonged survival of eosinophils, neutrophils, and macrophages; enhanced cytokine production; eosinophil degranulation
Interferon-alpha (IFN-α)	Monocytes/ macrophages, pDCs, and to a lesser extent B cells and NK cells	Inhibits viral replication
Interferon-beta (IFN-β)	Monocytes/macrophages	Similar to IFN-α
Interferon-gamma (IFN-γ)	$CD4^+$ Th1 cells, NK cells, and some $CD8^+$ cells	Differentiation; activation to express FcγR, MHC classes I and II, nitric oxide synthase, IL-1, and TNF in macrophages; shift of Th2 to Th1; growth and expression of IL-2R; increased cytotoxicity; activation of $CD8^+$ cells and NK cells
Interleukin-1 (IL-1)	Monocytes/macrophages	Cytokine production; cellular cytotoxicity; cytokine production; differentiation, proliferation, and immunoglobulin production; acute phase reactant
Interleukin-2 (IL-2)	$CD4^+$ cells	Clonal expansion of Ag-specific cells; differentiation and cytokine expression; maturation of $CD8^+$ cells; promotes T-cell maturation and growth; critical for Tregs
Interleukin-3 (IL-3)	T cells	Proliferation and differentiation of hematopoietic stem cells
Interleukin-4 (IL-4)	$CD4^+$ cells (Th2 cells)	Growth and activation of T and B cells; production of MHC class II, IL-6, TNF, CD23, CD72; switch factor for IgE; enhances IgE, IgG1, and IgG4 and inhibits IgM, IgG2, and IgG3 production; inhibits IFN-γ production; enhances IL-5 production
Interleukin-5 (IL-5)	$CD4^+$ cells	Proliferation, chemoattraction,

		adhesion, activation, enhanced survival, and degranulation of eosinophils
Interleukin-6 (IL-6)	Monocytes/ macrophages	Acute phase reactant; activates B cells to mature into plasma cells; switch factor for IgG1 and IgA; inhibits LPS; stimulates IL-1 and TNF-α production
Interleukin-7 (IL-7)	Bone marrow stromal cells and thymic stromal cells	Proliferation of progenitor B cells; proliferation of activated T cells
Interleukin-8 (IL-8)	Macrophages	Neutrophil chemotactic factor and histamine-releasing regulatory factor
Interleukin-9 (IL-9)	T cells	Enhances responses of B cells to IL-4, promotes mucus production and mast cell proliferation
Interleukin-10 (IL-10)	Murine $CD4^+$ Th2; human $CD4^+$, Th1, Th2, and $CD8^+$ cells (inhibited by IL-4 and IFN-γ)	Differentiation of monocytes to macrophages; inhibits expression of MHC class II and many adhesion molecules; inhibits IFN-γ and TNF production, resulting in switch of T-cell differentiation from Th1 to Th2
Interleukin-11 (IL-11)	Bone marrow stromal cell	Similar to IL-6
Interleukin-12 (IL-12)	Monocytes/macrophages	Activates NK cells; stimulates IFN-γ and TNF-α production by Th-1 cells; inhibits IL-4, IL-5, and IL-10 production by Th2 cells
Interleukin-13 (IL-13)	$CD4^+$ Th2 cells	Similar to IL-4; enhances production of MHC class II and integrins; reduced production of IL-1 and TNF; profibrotic
Interleukin-15 (IL-15)	Monocytes/macrophages	Proliferation; increased cytotoxicity; expression of ICAM-3; acts on T cells and NK cells
Interleukin-17 (IL-17)	$CD4^+$ cells	Autocrine proliferation and activation of $CD4^+$ cells
Interleukin-18 (IL-18; IFN-γ-inducing factor)	Macrophages, Kupffer cells	Similar to IL-12; inhibits IgE production by increasing IFN-γ
Interleukin-22	T cells, NK cells	Primarily on nonimmune, tissue

(IL-22)		cells; prevents hepatocyte apoptosis, induces antimicrobial peptides in skin, promotes keratinocyte proliferation
Interleukin-23 (IL-23)	Dendritic cells	Similar to IL-12, but acts preferentially on memory T cells, stimulates differentiation of naïve T cells to Th17 cells, roles in angiogenesis
Interleukin-25 (IL-25, IL-17E)	Epithelial cells, mast cells, eosinophils, basophils	Promote/sustain Th2 immune response
Interleukin-31 (IL-31)	Th2-type $CD4^+$ T cells	Acts on tissue monocytes and epithelial cells, implicated in driving T-cell homing to the skin in atopic dermatitis
Interleukin-33 (IL-33)	Epithelial cells, macrophages, DCs	Increases cytokine production from Th2 cells
Platelet-derived growth factor (PDGF)	Platelet α granule; monocytes/ macrophages	Proliferation; chemoattractant for fibroblasts; active in wound healing, atherogenesis, and airway remodeling
Stem cell factor (SCF) (c-kit ligand, mast cell growth factor)	Bone marrow stroma; fibroblasts	Chemoattractant for mast cells, with IL-3 stimulates growth; also has histamine-releasing activity
Transforming growth factor-beta (TGF-β)	Macrophages, epithelium, eosinophils, mast cells, Treg	Inhibits IL-2-stimulated growth; switch factor for IgA but inhibits IgM/IgG production; counteracts IL-4 stimulation of IgE; inhibits cytotoxicity; profibrotic
Tumor necrosis factor-alpha (TNF-α)	Monocytes/ macrophages	Enhanced apoptosis through DNA fragmentation; induces MHC classes I and II and adhesion molecule expression; cytotoxicity; effects are similar to IL-1
Thymic stromal lymphopoietin (TSLP)	Epithelial cells	Upregulate the costimulatory molecule OX40 ligand on DCs to enhance Th2 responses

Ag, antigen; NK, natural killer; CD, clusters of differentiation; IL, interleukin; Th, T helper; LPS, lipopolysaccharide; MHC, major histocompatibility complex; ICAM, intracellular adhesion molecule; TNF, tumor necrosis factor; IgG, immunoglobulin G.

(Modified from Kircher S, Marquardt D. Introduction to the immune system. In: Adelman DC, Casale TB Corren J, eds. Manual of Allergy and Immunology, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2002:1–23.)

a. Th1 cells. Th1 cells are primarily involved in cell-mediated pathogen clearance and delayed-type hypersensitivity. In humans, Th1 cells produce IL-2 and IFN-γ. Differentiation to the Th1 subtype is dependent on the transcription factor T-bet. IL-12 production by DCs leads to STAT4 activation and increased IFN-γ production, resulting in enhanced Th1 effector functions. Deficiency of the transcription factor T-bet skews T cells toward a Th2 response. IFN-γ reciprocally regulates Th2 cells by inhibiting the production of IL-4.

b. Th2 cells. The Th2 subset of $CD4^+$ T cells are characterized by production of IL-4, IL-5, and IL-13 but have been shown to also produce IL-9, IL-10, and TNF-α. Th2 immunity is important in driving B-cell proliferation and antibody responses. Differentiation to a Th2 subtype is dependent on IL-4 and STAT6 activation, leading to GATA-3 transcription factor upregulation and induction of Th2 cytokine production pathways while inhibiting Th1 cytokine production. Additionally, the TNF family member costimulatory member OX40 ligand is required for Th2 cell differentiation after interaction with TSLP-stimulated DCs. Th2 cells are phenotypically identified by

expression of the receptors, CRTH2 (prostaglandin D2-R) and ST2 (IL-33R). Th2-type responses are central to pathogenesis of allergic disease and critical to antiparasitic immunity.

c. Th17 cells. Th17 cells are $CD4^+$ T cells that produce IL-17A, IL-17F, and IL-22. Their differentiation and survival is dependent on TGF-β, IL-6, IL-21, and IL-23 and is regulated by the retinoic acid–related orphan receptor-γt (RORγt) and STAT3 transcription factors. IL-17 is important in the recruitment and proliferation of neutrophils and has a role in defense against bacterial and fungal infections. Mutations in the STAT3 DNA binding domain are responsible for one form of hyper-IgE syndrome (HIES) characterized by multiple skin abscesses and other infections, abnormal facies, skeletal problems, and rashes. These patients have a near absence of Th17 cells.

d. Regulatory T cells. Regulatory T cells (Tregs) are a subset of $CD4^+$ cells that suppress inflammatory responses and prevent autoimmunity. Tregs are classified as either natural Tregs or inducible Tregs. Natural Tregs develop in the thymus and are dependent on IL-2 for survival and are frequently identified by surface expression of CD25, the high-affinity IL-2 receptor, as well as expression of the transcription factor FoxP3. Inducible Tregs develop from naïve $CD4^+$ cells in the periphery and are dependent on TGF-β. Inducible Tregs also express FoxP3 that drives their suppressive function. Mutations in FoxP3 are responsible for the disease **immune dysregulation, poly-endocrinopathy, enteropathy, X-linked syndrome** (IPEX).

e. Other T-cell subtypes (Th9, Th22). More recently, additional T-cell subsets have been described that are distinct from Th1, Th2, and Th17 cells. These include Th9 and Th22 subsets. Th9 cells are IL-9-producing $CD4^+$ T cells that differentiate in the presence of IL-4 and TGF-β and minimally produce other Th2 cytokines. Th9 cells may represent a distinct lineage or perhaps a subset of Th2 cells. The transcription factor PU.1 has been implicated in Th9 development. IL-9 contributes to mucous production in the airway, mast cell proliferation, and propagation of allergic inflammation. Th22 cells differentiate in the presence of TNF-α and IL-6 and produce large quantities of IL-22 that acts primarily on nonimmune cells. Th22 cells have been implicated in the pathogenesis of skin disorders including atopic dermatitis, contact dermatitis, and psoriasis. The identification of these new subsets also led to the realization that T-cell subsets may display much greater heterogeneity and plasticity than originally recognized.

V. INDUCTION AND RESOLUTION OF INFLAMMATORY RESPONSES

A. Adhesion molecules. Adhesion molecules are surface molecules expressed throughout the immune system as well as on cells that interact with immune cells, such as endothelial cells, fibroblasts, and platelets. They play a critical role in leukocyte differentiation, cell–cell interactions, and trafficking. Three major families of adhesion molecules exist: integrins, selectins, and the immunoglobulin superfamily.

1. Integrins. Integrins expressed by leukocytes exist primarily as het-erodimers formed from 18 alpha-subunits and 8 beta-subunits that can dimerize to form 24 different integrins,

adding to the diversity of ligand recognition in the immune system, while permitting tissue specificity. The integrins regulate leukocyte adhesion in response to cytokines and chemokines, which alters either their affinity for ligands or their clustering on the cell surface.

2. **Selectins.** The selectins are C-type lectins that bind glycoproteins and glycolipids. L-selectin (CD62L) on leukocytes, E-selectinon cytokine-stimulated endothelial cells, and P-selectin stored in granules in endothelial cells and platelets mobilize to the surface after activation. The selectins are critical for leukocyte tethering to inflamed endothelium.
3. **Immunoglobulin superfamily.** The immunoglobulin superfamily includes the intracellular adhesion molecule (ICAM) subfamily, vascular cell adhesion molecule I (VCAM-1), and junctional adhesion molecules. ICAM-1 is expressed on endothelium, airway epithelium, and immune cells and is induced by proinflammatory cytokines IL-1β and TNF-α. ICAM-1 expressed by endothelium binds to the integrin complex CD11a/CD18 (LFA-1) on leukocytes to mediate leukocyte firm adhesion. Deficiency of CD18 is responsible for the primary immunodeficiency leukocyte adhesion deficiency 1 (LAD 1) characterized by peripheral blood leukocytosis, cold abscesses, and delayed separation of umbilical stump. ICAM-1 is also the receptor for human rhinovirus.

The expression of different adhesion molecules can be cell-specific and contribute to selective recruitment of a particular leukocyte. For example, the integrin VLA-4 is expressed by eosinophils and not neutrophils and binds to VCAM-1 expressed by endothelium, allowing for selective eosinophil but not neutrophil recruitment. Another example is receptors that contribute to the selective homing of lymphocytes to different tissues. Lymphocytes that migrate through peripheral lymph nodes express L-selectin, which recognizes peripheral-node addressins present in peripheral lymph nodes. In contrast, lymphocytes that migrate through the gut express α4b7-integrin, which recognizes mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1) on venules of the intestinal lamina propria.

B. Leukocyte endothelial adhesion. Leukocyte endothelial adhesion is a stepwise process that includes **leukocyte rolling, adhesion, and transendothelial migration**. Endothelial cells do not normally express adhesion molecules, and thus, under baseline conditions, leukocytes circulate through the bloodstream without exiting the vasculature. However, at sites of tissue inflammation, endothelial cells are induced to upregulate adhesion molecules, allowing for the localization of leukocytes to the site of tissue inflammation. The initial step of leukocyte rolling on endothelium depends on binding of selectins, which tethers cells to the endothelium for short periods of time and is dependent upon shear forces from the circulating blood. The release of initial bonds and formation of new bonds along the endothelial surface sustains the rolling phenomenon at sites of inflammation where activated endothelial cells enhance their expression of selectins and selectin ligands. Before the leukocyte can pass through the endothelium, the rolling cell must firmly adhere to the endothelium, and this step is mediated by immunoglobulin family members such as ICAM-1 and VCAM-1. Binding leads to strengthening of cellular adhesion through cytoskeletal changes and recruitment of additional adhesion molecules. During transendothelial migration, leukocytes pass through the intercellular junctions in endothelium. The final step of tissue entry of leukocytes from the blood vessel is termed **chemotaxis**.

Chemotaxis is the directed migration of leukocytes along a chemokine gradient from the endothelium to the site of tissue inflammation. Eotaxin is an example of an eosinophil chemoattractant and IL-8 an example of a neutrophil chemoattractant. The importance of adhesion molecules to leukocyte trafficking is suggested from diseases associated with defects in leukocyte integrin adhesion molecules (e.g., LAD) and reduced neutrophil adhesion that lead to increased susceptibility to infection.

C. Cell death and immunity (apoptosis, pyroptosis, and autophagy). Regulation of cell death is essential in immunity, both in the initial development of self-tolerance and in prevention of host tissue damage following inflammation. Apoptosis is one form of programmed cell death, characterized by cell shrinkage, nuclear fragmentation, and the formation of plasma-membrane blebs. The two pathways by which apoptosis occurs include the death-receptor pathway and the Bcl-2-regulated mitochondrial pathway mediated by gamma radiation, oxygen radicals, or DNA damage that ultimately leads to mitochondrial injury. In the death receptor–mediated pathway, a ligand such as Fas, TNF, or TNF-related apoptosis-inducing ligand binds to the death receptor, recruiting FAS-associated death domain and subsequently caspase 8 and caspase 3. In the Bcl-2-regulated intrinsic pathway, damaging stimuli activate proapoptotic, BH3, members of the Bcl-2 family, ultimately leading to caspase 9 activation and then caspase 3 activation. Activation of caspase 3, and subsequently caspase 6 and caspase 7, leads to synchronous cleavage of proteins in many cell compartments, resulting in the characteristic morphologic changes and blebbing by which apoptosis was first identified. Abnormalities in apoptosis increase susceptibility to autoimmune diseases by failing to delete autoreactive lymphocyte clones. The most severe form is autoimmune lymphoproliferative syndrome, in which a genetic defect in Fas ligand or its receptor leads to massive lymphadenopathy, splenomegaly, and cytopenias.

More recently, autophagy and pyroptosis have been implicated in inflammation and immune responses. **Autophagy** is the homeostatic process by which cells break down their own components. During autophagy, autophagosomes fuse with lysosomes, and degradation of contents ensues. Innate immune signals through PRRs such as TLRs and NOD-like receptors as well as the cytokines TNF-α and IFN-γ can induce autophagy. In turn, proteins involved in autophagy appear to regulate both innate and adaptive immune responses including resistance to a broad array of pathogens. **Pyroptosis** is characterized by inflammatory cell death dependent on caspase-1, an enzyme responsible for activation of proinflammatory cytokines IL-1β and IL-18. Pyroptosis appears to be an important mechanism of host defense against the flagellin-expressing bacteria *Salmonella*. The roles of autophagy and pyroptosis in immune responses remain promising areas of future investigation.

VI. HYPERSENSITIVITY REACTIONS.

Although the function of the immune system is protection of the host from foreign antigens, abnormal immune responses can lead to tissue injury and disease broadly defined as hypersensitivity reactions. Gell and Coombs classified the mechanisms of immune-mediated tissue injury into four distinct types of reactions, types I to IV:

A. Type I reactions are immediate-type hypersensitivity reactions. Antigen binding to preformed IgE antibodies present on the surface of mast cells or basophils results in release of preformed and newly synthesized inflammatory mediators, for example, histamine, leukotrienes, cytokines, proteases, arachidonic acid metabolites, and enzymatic mediators,

which produce the clinical manifestations within minutes of antigen exposure. Examples of type I diseases include anaphylactic shock, allergic rhinitis, allergic asthma, and acute drug allergic reactions.

B. **Type II reactions involve the binding of either IgG or IgM antibody to cell-bound antigens.** Antigen–antibody binding results in activation of the complement cascade or ADCC and destruction of the host cell. Erythroblastosis fetalis (Rh hemolytic disease of the newborn) and autoimmune hemolytic anemia are examples of type II reactions leading to cell death. A subset of type II reactions exists in which IgG antibodies form against host cell surface receptors, with subsequent inhibition of receptor function or uncontrollable activation. Examples include autoimmune hyperthyroidism and myasthenia gravis. Note that in this subset of type II reactions, cytolysis does not occur.

C. **Type III or immune complex–mediated reactions**. Type III reactions occur when immune complexes are formed after antigens bind to antibodies. Normally, these complexes are cleared from the circulation by the phagocytic system. However, under circumstances where there are increased quantities of circulating complexes in the presence of vasoactive amines, which increase vascular permeability, the deposition of immune complexes in vascular endothelium or peripheral tissues is favored. Immune complex deposition leads to complement activation, anaphylatoxin generation, neu-trophil recruitment, phagocytosis, and ultimately host tissue injury. Serum sickness, poststreptococcal glomerulonephritis, and systemic lupus erythematosus are examples of type III reactions.

D. **Type IV reactions are delayed-type hypersensitivity and are cell mediated**. Unlike the other types of hypersensitivity reactions, antibodies do not play a role in type IV reactions. Since the original Gell and Coombs' classification, this class of reactions has been further subdivided on the basis of the effector cells perpetuating the reaction. **Type IVa is the classic type IV reaction** in which Th1 $CD4^+$ T cells drive monocyte and macrophage activation. The tuberculin skin test reactions and contact dermatitis remain classic examples of this type of reaction. In **Type IVb reactions**, T cells drive eosinophilic inflammation via a Th2 response, leading to maculopapular exanthems. **Type IVc reactions** are characterized by $CD4^+$ T-cell and $CD8^+$ T-cell cytotoxicity via perforin, granzyme B, and Fas ligand and can contribute to contact dermatitis, maculopapular, pustular, and bullous rashes as seen in Stevens-Johnson syndrome and toxic epidermal necrolysis. Finally, **Type IVd** reactions involve T-cell recruitment of neutrophils through CXCL8 and GM-CSF to sites of sterile inflammation. This type of reaction is seen in Behçet's disease. It should be noted that in most clinical reactions, however, these subclasses may not be as well defined, and different type IV reactions may occur together.

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2

Immediate Hypersensitivity: Approach to Diagnosis

Nkiruka U. Erekosima and Sarbjit S. Saini

I. BACKGROUND: HISTORICAL PERSPECTIVE OF IMMUNOGLOBULIN E

Nearly a century ago, Portier and Richet reported a paradoxical immunologic effect when trying to enhance the resistance of dogs to sea anemone toxin by injecting the dogs with the toxin. Rather than conferring the expected protection, when reinjected weeks later with minute amounts of the same toxin, several animals died within minutes of cardiorespiratory collapse. To describe this phenomenon, they coined the term **anaphylaxis** (meaning antiprotection). Subsequent studies determined that these reactions required prior exposure to the foreign substance and a period of weeks to manifest the response. They also found that anaphylactic sensitivity could be transferred from one animal to another by injecting or infusing a serum-derived factor, initially referred to as **reagin**. Soon thereafter, studies in humans revealed that injection of serum from an anaphylactically sensitive individual into a nonsensitive individual (**passive transfer**) led to local sensitization (transfer of a wheal-and-flare reaction) in the recipient at the cutaneous site. The passive transfer experiment, first performed by **Prausnitz and Kustner**, and now referred to as the PK test or reaction, gave the first indication that allergic hypersensitivity resulted from a serum protein. This type of response became known as **immediate hypersensitivity** due to the rapidity of the reaction. However, the composition of reagin remained a mystery until the 1960s, when Ishizaka and Ishizaka purified and identified **immunoglobulin E (IgE)**, establishing that reagin was an antibody molecule. It is now clear that the presence of specific IgE antibodies represents the single most important determinant of allergic sensitivity. Synthesis or passive transfer of IgE antibodies sensitizes the recipient for both the immediate allergic response and any subsequent reactions. Today, the term **allergen** refers to a protein, typically a common innocuous antigen that elicits IgE antibody production. **Allergy** refers to the clinical manifestations of IgE-dependent immunologic reactions, whereas **atopy** is used to describe the genetic tendency to generate IgE responses.

II. ANTIGEN CHARACTERISTICS

Antigens. For a substance to generate an immune response, it must be presented to the immune system in an appropriate fashion. Characteristics of the antigen can determine whether the immune system develops an antibody response of a particular class or whether an antibody response is generated at all. For example, so-called T-cell–independent antigens such as polysaccharides do not typically give rise to IgE antibodies. Thus, the nature of the antigen is an important determinant of the host response. Although a complete understanding of what makes an antigen an allergen has not been achieved, several general principles can be stated. Most common allergens (e.g., pollen, dust mites, animal dander) that cause airway symptoms in humans are proteins with a molecular

weight of 10 to 20 kDa, are highly water-soluble, and can act as complete allergens. Repeated, low-level exposure to these proteins (typically in the submicrogram range) diffusing across mucosal surfaces is particularly efficient at inducing an IgE response. Host characteristics are also key in generating IgE responses, given that about 20% of the exposed population, that is, those with the atopic trait, will generate IgE antibodies. Some of the most prevalent aeroallergens, such as dust mites (*Der p 1*, a cysteine protease), have enzymatic functions in their natural state. However, a clear association between the functional properties of an allergen and its **immunogenicity**, that is, the ability to generate immunologic responses in susceptible subjects, is lacking. It has also been difficult to identify common structural features among known allergenic proteins to allow predictions of the immunogenicity of novel peptides. However, the cross-reactivity of a protein with preexisting IgE antibodies to another allergen has been shown to be based on structural similarities and presents clinically, for example, in the **pollen-food allergy syndrome**. Here, the ingestion of labile proteins found in, for instance, fresh apples, can cross-react with an individual's existing birch pollen–specific IgE, leading to the occurrence of itching of the oral mucosa. Cooking the apple rapidly inactivates the cross-reactive allergen, thus eliminating the symptoms.

A. Complete protein allergens. By definition, proteins that are complete allergens have (i) the property to induce the production of IgE antibodies; (ii) the ability to elicit an allergic reaction or trigger symptoms in a sensitive host; and (iii) the property to bind IgE antibodies with sufficient numbers of antigenic determinants.

B. Incomplete protein allergens. An incomplete allergen is one that is able to elicit symptoms in a sensitive host but cannot independently generate an IgE antibody response. Commonly, these are low-molecular-weight drugs such as the β-lactam family of antibiotics. On the basis of studies with penicillin, the β-lactam molecule generates reactive metabolites in vivo that covalently bind to a number of the host's normal proteins, such as albumin. These reactive compounds are termed **haptens**, and by definition they must bind to other proteins (haptenate) in vivo to elicit an IgE response. Penicillin hapten–protein complexed allergens, also called major and minor determinants, have been identified and used for diagnostic skin testing. However, it has been difficult to establish standard skin testing reagents for the evaluation of other incomplete drug allergens, given the multiple pathways to generate drug intermediates and their potential for haptenization.

III. PRODUCTION OF IMMUNOGLOBULIN E

If many individuals are exposed to the same antigen by the same route, only a few develop IgE antibodies, and therefore only a minority of these people are at risk for allergic reactions upon reexposure. There is also the concept of asymptomatic sensitization; for example, 8% of the US population has a positive skin test to peanut, but < 1% have clinical manifestations of peanut allergy. Why only a minority of people make antigen-specific IgE and become allergic remains unknown. If such events are to occur, however, a distinct series of immunologic events must happen (Fig. 2-1). First, an allergen needs to cross an epithelial barrier. The epithelium can provide signals that favor allergic sensitization. The allergen is next internalized by antigen-presenting cells, such as dendritic cells (DCs), and, after processing, is presented to T lymphocytes. Recent studies have demonstrated that **thymic stromal lymphopoietin (TSLP)**, an

epithelial cell–derived cytokine, has an important role in initiating allergic inflammation (see Chapter 1, Section III, D), by polarizing DCs to drive T helper (Th2) cell inflammation. If an IgE antibody response is to occur, these events must take place in the presence of specific cytokines, the most important of which is interleukin (IL)-4 released by T lymphocytes and other cells. IL-4 is critical for the generation of the T lymphocytes (Th2 cells) themselves and for subsequent stimulation by these Th2 cells of B lymphocytes. If this stimulation occurs in the presence of IL-4 and IL-13, the B cells undergo immunoglobulin gene class switching, leading to their terminal differentiation into plasma cells that produce antigen-specific IgE antibodies. Generation of IgE-producing plasma cells is also facilitated by binding of CD40 ligand on the Th2 cell to CD40 on the B cell. Once plasma cells undergo these steps, they release the exact same antigen-specific IgE for the rest of their lives. This IgE secretion by plasma cells typically takes place at mucosal sites, but it can also occur in lymph nodes and other lym-phoid organs. Among immunoglobulins, IgE has several unique features. For example, unlike IgG, IgE cannot cross the placenta, and it does not bind complement. IgE contains an additional region in its heavy chain that makes the molecule uniquely capable of binding to specific IgE receptors. IgE is also heavily glycosylated, although the biologic significance of this is uncertain. Finally, although the presence of IgE correlates with allergic diseases, high levels of IgE are seen in other disorders, such as helminthic parasite infections, whereas low levels of serum IgE overlap between allergic and nonallergic persons.

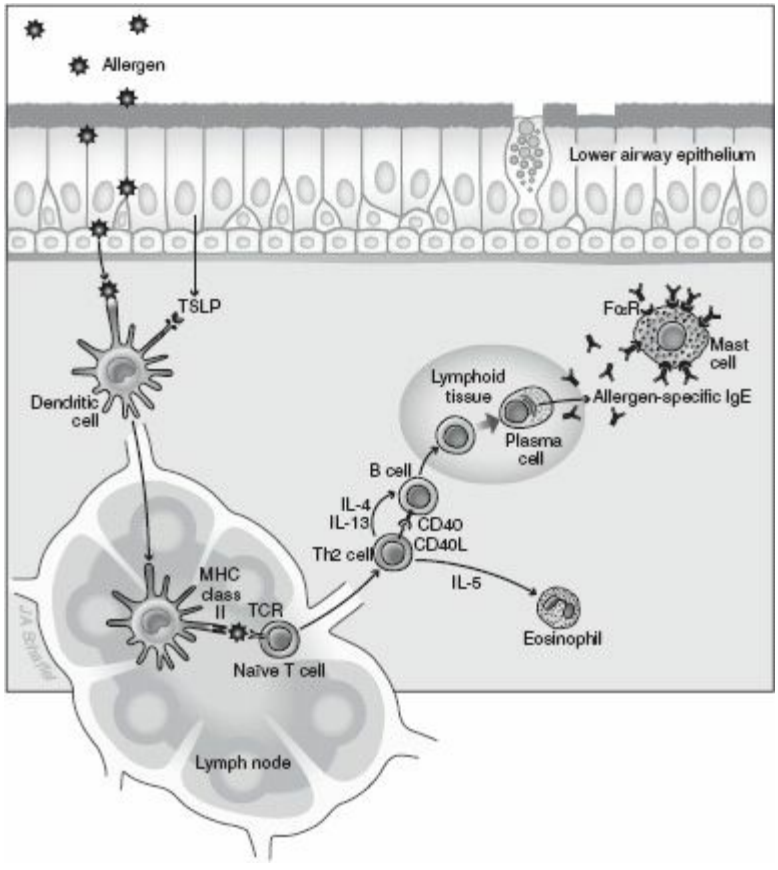

Figure 2-1. Allergen sensitization. Activation of the immune system by an antigen requires exposure such as may occur when allergen breaches a mucosal surface. TSLP, an epithelial cell–derived cytokine, polarizes DCs to drive allergic inflammation. Antigen-presenting cells such as DCs can ingest antigens in the tissue

and present digested peptide fragments via their major histocompatibility complex (MHC) immune recognition system. Activated antigen-presenting cells travel via the lymphatics to local lymph nodes and make contact with T cells whose specific antigen receptors recognize one of the peptides in their MHC class II. A productive interaction occurs, and the antigen-specific T lymphocyte is activated. Antigen-specific T cells are then capable of activating antigen-specific B cells to produce IgE antibodies either in primary or secondary lymphoid tissue or within the local tissue site. If the T cells are a subset referred to as Th2, that is, those associated with allergic inflammation, then the B cells will shift the isotype of immunoglobulin produced to the IgE isotype under the influence of unique cell–cell attachment (via clusters of differentiation 40 [CD40] and CD40 ligand) and cytokines, such as IL-4 or IL-13, produced by T cells, and will differentiate into IgE-producing plasma cells. Once released by plasma cells, antigen-specific IgE binds to high-affinity IgE receptors (FcεR) on mast cells and basophils, leading to sensitization of these cell types. Th2 cells also secrete the cytokine IL-5, which can activate eosinophils and prolong their survival in tissues. (From Jacqueline Schaffer, with permission).

IV. IgE RECEPTORS

Secreted IgE produced by allergen-specific B cells binds to specialized Fc receptors on the surface of mast cells and basophils throughout the body. Although free IgE has a short serum half-life (2 to 3 days compared to 21 days for IgG), IgE bound to the surface of mast cells can persist for several months. The **high-affinity IgE receptor (FcεRI)** expressed by human mast cells and basophils is a tetramer composed of one alpha, one beta, and two gamma chains. Despite the low serum concentration of IgE (typically in the nanogram per milliliter range), most surface FcεRI receptors are occupied, given that the dissociation constant is 1×10^{-10} M. The alpha chain binds to IgE at its third heavy chain constant domain, whereas the β and γ subunits of the receptor are involved in transducing signals generated by activation of the receptor complex (Fig. 2-2). The therapeutic anti-IgE antibody, omalizumab, designed for clinical use in allergic disease, takes advantage of this fact by binding to the third heavy chain of free IgE, competitively inhibiting IgE from binding to the alpha chain of FcεRI. The overall number of high-affinity receptor complexes on basophils ranges from a few thousand to 1 million molecules per cell and is positively related to the level of circulating free IgE as well as to levels of expression of the beta subunit. Both IgE levels and cytokines such as IL-4 and IL-9 are believed to enhance mast cell FcεRI expression. An alternate, trimeric high-affinity IgE receptor (composed of one α and two γ chains) occurs on monocytes, DCs, and Langerhans' cells, especially in allergic hosts; these cells utilize this receptor to capture antigen for eventual presentation by these cells to T cells. Dc IgE receptor–facilitated allergen presentation to T cells can be downregulated by omalizumab.

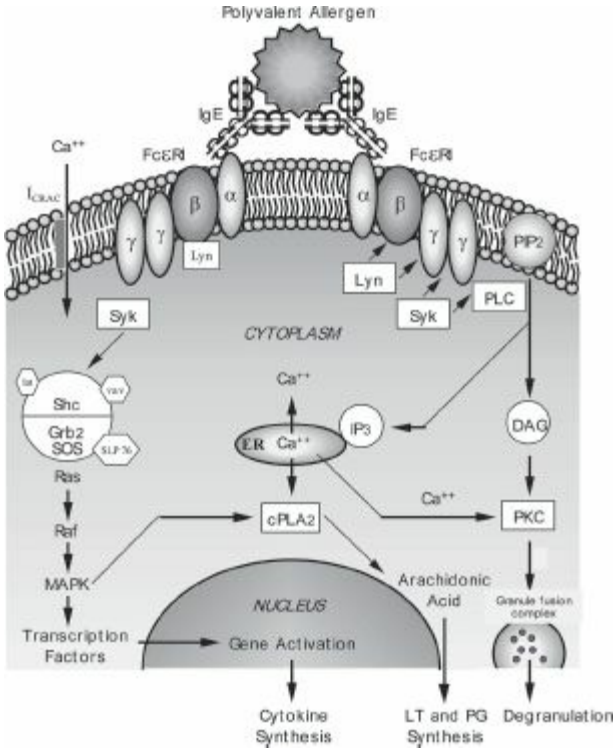

Figure 2-2. Cross-linking of immunoglobulin E (IgE) activates intracellular biochemical pathways. Once mast cells or basophils are sensitized by IgE binding to the FcsRI alpha chain, they can be activated by polyvalent allergen that cross-links adjacent receptors. See text on pages 36 and *37* for details.

Another receptor for IgE, termed FcεRII (or CD23), has low affinity for binding IgE, with a single transmembrane chain that is unrelated to FcεRI. CD23 binds to the Ce3 domain of IgE, which is different from the FcεRI binding site. Expression of CD23 is upregulated by IgE and IL-4. It is expressed as two different forms: CD23a and CD23b. CD23a is expressed constitutively on B cells, and CD23b is expressed on several cells, including monocytes, eosino-phils, DCs, Langerhans' cells, and platelets. CD23b is also inducible on B cells and some T cells by IL-4 or IL-13 stimulation. Activation of CD23 on B cells leads to multiple functions, including B-cell differentiation, regulation of IgE synthesis, apoptosis, activation of monocytes, and antigen presentation. CD23 also binds to other ligands, including the adhesion molecules CD11b and CD11c, and these interactions lead to other functions. CD23 can be cleaved by proteases to generate a soluble CD23 form, which is proinflammatory. *In vitro* studies of a monoclonal antibody that targets CD23, lumiliximab, demonstrate that lumiliximab leads to decreased Th2 responses and reduced IgE synthesis.

V. MEASUREMENT AND CLINICAL SIGNIFICANCE OF IgE

Measurement of allergen-specific IgE is determined by skin testing or by detection of allergen-specific IgE in serum (discussed further in **Chapter 20, Diagnostic Immunology**). Increased IgE levels are seen in individuals with atopic diseases. In general, individuals with atopic dermatitis tend to demonstrate higher IgE levels than those observed in other atopic conditions. Measurement of allergen-specific IgE in serum is particularly useful in specific clinical situations when skin testing cannot be performed. It can also be used to monitor disease activity in certain

conditions such as food allergy. Total serum IgE level is also useful for monitoring disease activity and response to therapy in patients with allergic bronchopulmonary aspergillosis. Elevated IgE levels are also present in several nonatopic conditions, such as parasitic infections, human immunodeficiency virus (HIV), certain autoimmune/inflammatory disorders, malignancies, and some primary immunodeficiency diseases.

Evidence for the role of human IgE in allergic disease has long been recognized by the ability to transfer allergen sensitivity by serum IgE (reaginic reactivity). More recently, trials of the humanized monoclonal anti-IgE, omali-zumab, which reduces free IgE levels in serum, have shown clinical benefits in subjects with allergic asthma, allergic rhinitis, airway allergen challenge models, and conditions of anaphylaxis (food and rush immunotherapy); however, omal-izumab is approved by the U.S. Food and Drug Administration (FDA) only for patients with moderate to severe persistent allergic asthma.

VI. MAST CELLS AND BASOPHILS

A. Origin and distribution. Mast cells and basophils can be identified microscopically by the presence of cytoplasmic granules that contain acidic molecules that take up basic dyes and stain metachromatically. Both cell types also bear high-affinity IgE receptors. They both originate from $CD34^+$ hematopoietic, pluripotent stem cells residing in the bone marrow but differ in their developmental stages. Undifferentiated mast cells migrate from the bone marrow to the connective tissues of mucosal and epithelial surfaces of the body. They subsequently mature and take up residence in close proximity to blood vessels, nerves, and body surfaces in contact with the external environment. Mast cells (and some basophils) also uniquely express high levels of c-kit, a receptor that binds the important growth factor, stem cell factor (SCF). The local tissue environment can provide SCF as well as influence mast cell mediator content, granule ultrastructure, and functionality, thus contributing to heterogeneity among mast cell populations (tryptase-positive or chymase/tryptase-positive cells). In contrast, basophils mature in the bone marrow under the influence of IL-3, differ from mast cells in bearing high levels of $CD123^+$ expression (receptor for IL-3), and reside in the circulation as mature, nondividing cells. Activated basophils express high levels of IL-4, IL-13, and CD40 ligand. In the past, basophils were thought to be a form of circulating mast cell but are now considered closer in lineage to eosinophils. Basophils can migrate to tissue sites in response to inflammatory stimuli, such as those generated during the late phase of an allergic response (Fig. 2-3). Seasonal allergen exposure can cause an increase in the number of circulating basophils and tissue mast cells. Local application of steroids, such as in the nose of rhinitis patients, will blunt the increase in mast cells that is normally observed during the pollen season.

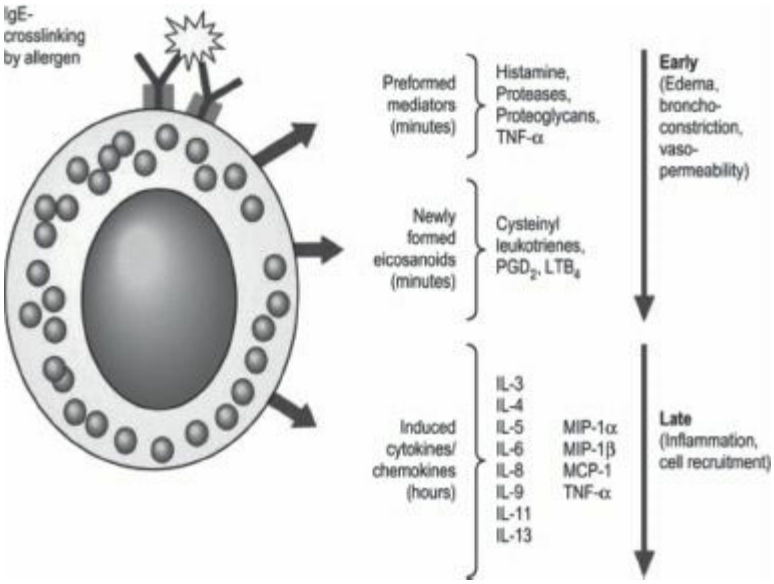

Figure 2-3. Mediators released from mast cells upon IgE-mediated activation. See description on pages 37 and 38 for details. (Reproduced from Hsu FI, Boyce JA. Biology of mast cells and their mediators. In: Adkinson NF, Bochner BS, Busse WW, et al., eds. *Middleton's allergy: principles and practice.* Philadelphia, PA: Elsevier, 2009:311–328, with permission.)

B. Pathways of mast cell and basophil mediator release. Allergen cross-linking of IgE bound to the surface of mast cells and basophils leads to cellular activation, degranulation, and inflammatory mediator release. In addition to allergen, experimental antibodies that can cross-link cell-bound IgE or FcεRI receptors can also activate mast cells and basophils. In either case (allergen or cross-linking antibodies), bridging of as few as 1% of the total surface FcεRI (about 300 to 500 receptors) can be sufficient to activate the cells.

A number of IgE-independent pathways for activation of mast cells and basophils also exist. Most of these depend on the influx of calcium for cellular activation. Examples of in vivo triggers are drugs such as opiates (for skin mast cells), aspirin, and other nonsteroidal anti-inflammatory drugs (NSAIDS), smooth muscle relaxants, and intravenous radiocontrast dyes. Examples of *in vitro* agents are calcium ionophore and compound 48/80 (the latter for mast cell activation). There are also numerous biologic inflammatory stimuli that can activate or potentiate mediator release, including histamine-releasing factors, products of complement activation (C3a, C5a), nerve-related peptides (tachykinins, nerve growth factor, calcitonin gene-related peptide), adenosine triphosphate, IL-1, IL-3, and several chemokines. In addition, skin mast cells in certain subjects can be activated by a variety of physical stimuli (such as cold temperature, pressure, sunlight, heat, or exercise) to produce urticaria.

C. Releasability. The wide variation noted in the extent of histamine release from basophils of different individuals has been termed releasability. Factors that determine the sensitivity of basophils or mast cells to allergen activation, or the magnitude of their mediator release, are still not clear. There is some evidence that factors such as the ratio of allergen-specific IgE to total IgE, the affinity of IgE for the allergen, and levels of Syk (a tyrosine kinase necessary for proper signal transduction) influence releasability. About 5% to 10% of people have basophils that fail to release any histamine after IgE receptor cross-linking. These "non-releaser" basophils appear to be deficient in Syk (see Fig. 2-2). Allergen immunotherapy leads to a higher threshold for allergen-induced baso-phil mediator release and may be one of the mechanisms of action of this form of treatment. In cultured mast cell systems, the induction of greater numbers of FcεRI receptors by either IL-4 or IgE leads to increased sensitivity to allergen and increased

magnitude of mediator responses, whereas treatment with omalizumab appears to counteract these effects. However, similar effects of increased FcεRI expression or surface-bound IgE on basophil mediator responses have not been observed.

D. Biochemical signaling pathways triggered by multivalent allergen. Antigen-induced FcεRI aggregation leads to the stimulation of a complex cascade of intracellular signaling events. Although these events have been extensively studied, the order of events and the exact molecules that participate in each cell type are not fully known. Figure 2-2 depicts a possible schema for FcεRI-related signaling events. The bridging of adjacent surface-bound IgE molecules by polyvalent allergen allows receptor-associated Src family kinase, Lyn, to phos-phorylate the receptors β and γ subunits and initiate signaling. The tyrosine kinase Syk is then recruited to the receptors phosphorylated γ chain, and this is followed by the assembly of a macromolecular signaling complex containing adaptor molecules (Grb2, LAT, Slp76) and enzymes (Vav, SOS) that ultimately lead to the endpoints of granule secretion, lipid metabolite generation, and synthesis of cytokines. One proposed pathway involves Syk-mediated phos-phorylation of Btk, which activates phospholipase C (PLC). PLC in turn hydrolyzes phosphatidylinositol-bisphosphate (PIP_2, found in the plasma membrane) to inositol 1,4,5-triphosphate (IP) and 1,2-diacyl glycerol (DAG). IP_3 functions by binding to receptors on the endoplasmic reticulum, mobilizing internal calcium stores, leading to a transient rise in the cytosolic concentration of calcium. Emptying of intracellular stores results in the opening of a plasma membrane channel (I_{CRAC}), resulting in the sustained calcium flux needed for secretion. Both DAG and calcium can activate the protein kinase C (PKC) family of enzymes. PKC is able to phosphorylate many substrates including myosin light-chain kinase, which may act to change the cytoskeleton to permit degranulation. A separate pathway traced to the FcεRI complex activation involves the p21ras molecule leading to downstream activation of the mitogen-activated protein kinases (MAPK). The p21ras pathway is common to several receptors and involved in numerous cell functions including the activation of transcription factors that can enter the nucleus to activate cytokine genes. Elevations in intracellular calcium and phosphorylation of other MAPK can activate cytoplasmic phospholipase A_2 ($cPLA_2$). $cPLA_2$ cleaves membrane phospholipids to generate arachidonic acid and eventually leads to synthesis of prostaglandins (PGs) and leukotrienes (LTs).

It is important to note that several agents can inhibit cellular degranulation, including ethylenediaminetetraacetic acid (by calcium chelation), cyclic adenosine monophosphate (cAMP), colchicine, cromolyn, beta-agonists, and corticosteroids (true for basophils but not mast cells). Therapeutic drugs that can block mediator release include those that target cAMP by either increasing its levels (e.g., beta-adrenergic agonists) or preventing the breakdown of cAMP by inhibiting phosphodiesterases (e.g., theophylline). Although it is known to inhibit degranulation, the specific intracellular targets of cromolyn are not understood. Some therapeutics that are under development or in early clinical testing specifically inhibit events early in the signaling cascade, such as the activation of Lyn or Syk tyrosine kinases.

E. Clinical significance

Mast cells. Mast cells serve as critical sensor cells between the environment and the host. They are initiator cells that release many mediators thought to be relevant in the pathogenesis

of allergic diseases, including anaphy-laxis, allergic rhinitis, and allergic asthma. Activating mutations in c-kit lead to mastocytosis, which is characterized by increased mast cell number and clinical features that resemble some of those in anaphylaxis. Evidence for mast cell involvement can be supported by the detection of elevated tryptase levels in serum. The monoclonal mast cell activation syndrome is characterized by aberrant, clonal mast cell populations.

Basophils. The function of basophils in normal physiology remains unknown. However, they are thought to contribute to host defense, especially against parasites. Basophils are known to be the predominant source of IL-4 in peripheral blood mononuclear cells that have been activated by allergen or helminthic parasites. They also release other mediators important in allergic disease, including histamine, LTC4, and IL-13. Basophils have also been identified in cutaneous, nasal, and pulmonary sites both in allergic disease as well as in late-phase responses following experimental allergen challenge. More recent models using IL-4 reporter mice and those deficient in basophils suggest a more prominent role for this cell in the initiation of allergic inflammation and in immunity to helminth and tick infections.

VII. IMMEDIATE HYPERSENSITIVITY: PATHOPHYSIOLOGY

The major consequences of allergen cross-linking IgE bound to the surface of mast cells and basophils are cellular activation, degranulation, and inflammatory mediator release. The complex of symptoms associated with **immediate hypersensitivity** begins minutes after allergen exposure and is linked to release of preformed and rapidly generated mediators from mast cells and basophils. The clinical consequences of this rapid reaction are called the **early-phase response (Fig. 2-3)**. Depending on the site and circumstances of allergen exposure, symptoms can range in severity from sneezing and rhinorrhea following pollen inhalation (as seen in allergic rhinitis) to anaphylaxis following systemic allergen exposure (e.g., drug, insect sting, or food), leading to possible death. The implicated mediators are typically classified based on their pattern of release and include those that are preformed in granules and released by exocytosis (e.g., histamine, tryptase), those that are rapidly synthesized from membrane lipids (e.g., prostaglandins, LTs, platelet-activating factor [PAF]), and, lastly, cytokines that are synthesized and released over several hours. The nature of each mediator, its cellular source, and main action are summarized in Table 2-1.

Table 2-1 Mast Cell and Basophil Mediators Released by IgE Cross-linking

Mediator	Cell	Actions
PREFORMED		
Histamine	MC, B	Vasodilatation; increased vascular permeability; smooth muscle contraction; bronchospasm; mucus secretion; pruritus; P-selectin induction; fibroblast proliferation
Proteoglycans		
Heparin	MC	Anticoagulant; storage matrix
Chondroitin sulfate	MC, B	Probably storage matrix
Neutral proteases		
Tryptase	MC_T, MC_{CT}, B*	Generate C3a and bradykinin; degrades fibrinogen and neuropeptides such as VIP; induces epithelial IL-8 production; stimulates angiogenesis
Chymase	MC_{CT}, B*	Degrades extracellular matrix; stimulates angiogenesis
Carboxypeptidase A	MC_{CT},	Undefined; acts in concert with other proteases
Lysosomal acid hydrolases		
β-Hexosamidase	MC	Function unclear
β-Glucuronidase	MC	Cleaves tissue matrix
Preformed cytokines		
TNF-α, IL-16	MC	*See CYTOKINES next page*
NEWLY FORMED		
Arachidonic acid metabolites		
LTB_4	MC	Neutrophil and effector T cell chemoattractant
LTC_4	MC, B	Bronchoconstriction; mucus secretion; increased vascular permeability; eosinophil chemoattractant (formerly SRS-A)
PGD_2	MC	Bronchoconstriction; mucus secretion; edema; vasodilation; increased vascular permeability; chemoattractant for Th2 cells, eosinophils, and basophils
PGF_2	MC	Smooth muscle contraction
PAF	MC	Chemoattractant for eosinophils and neutrophils; platelet aggregation; increased bronchoconstriction and vascular permeability

IL-6	MC	Increased IgE synthesis
IL-8	MC, B	Neutrophil chemoattractant
IL-4	B, MC	Induction of endothelial VCAM-1, IgE production by B cells, differentiation of Th2 cells, increased FcεRI and CD23, epithelial eotaxin; mucus production
IL-13	B, MC	Induction of endothelial VCAM-1, IgE production, mucus secretion, epithelial eotaxin
IL-16	MC	Chemoattractant for $CD4^+$ lymphocytes, eosinophils, and monocytes
IL-33	MC	Activation of basophils, increased mast cell proliferation and cytokine production
GM-CSF, IL-5	MC	Eosinophil growth, activation, survival
TNF-α	MC	Induction of endothelial adhesion molecules, epithelial chemokines, mucus secretion, leukocyte cytokine secretion, activation of neutrophils, recruitment of other effector cells
CHEMOKINES		
MCP-1	MC	Monocyte and T cell chemotaxis
MIP-1 alpha	MC, B	Macrophage differentiation, neutrophil chemotaxis, and cytotoxicity
MIP-1 beta	MC‡	Chemotaxis of monocytes
RANTES	MC‡	Chemotaxis of eosinophils, basophils, lymphocytes

MC_{CT}, chymase and tryptase–containing mast cell, found in skin, blood vessels, and intestinal sub-mucosa; MC_T, tryptase-containing mast cell, typically found in lung, nasal cavity, intestinal mucosa; B*, extremely low levels of this mediator have been found in basophils (1%of that in mast cells); MC‡, MIP-1 β and RANTES were found in HMC-1, a human mast cell leukemia cell line; IgE, immunoglobulin E; LT, leukotriene; PG, prostaglandin; PAF, platelet-activating factor; IL, interleukin; VIP, vasoactive intestinal peptide; SRS-A, slow-reacting substance of anaphylaxis; VCAM-1, vascular cell adhesion molecule-1; Th2, T helper 2; CD, clusters of differentiation; GM-CSF, granulocyte macrophage colony–stimulating factor; TNF, tumor necrosis factor; MCP, monocyte chemotactic protein; MIP, macrophage inflammatory protein; RANTES, regulated upon activation, normal T cell expressed and secreted

One classic manifestation of immediate hypersensitivity is the wheal-and-flare response to allergen in the skin. The diagnostic skin test is based on the ability of IgE-sensitized skin mast cells to respond to specific allergen exposure within minutes by releasing vasoactive mediators (such as histamine) at the site of allergen application, an example of the immediate or **early-phase response**. Injection of histamine into the skin initially causes vascular leak leading to a raised area or "wheal" from local edema. This is followed by a neuronal reflex leading to increased vasodilatation and vascular permeability at the periphery of the wheal, yielding the erythema or "flare" response.

Following allergen exposure of sensitive individuals, acute allergic reactions subside within minutes but can often be followed hours later by a second inflammatory response termed the **late-phase response**. Approximately 50% of subjects challenged with allergen in the skin, nose, or lungs also develop a reaction 4 to 12 hours after allergen exposure. This late-phase response is characterized by recurrence of clinical symptoms as well as the local influx of circulating leukocytes such as eosinophils, lymphocytes, and basophils to the tissue in response to the mediators released during the early phase. Mediators released from eosinophils during the late phase contribute to tissue damage. In the skin, the late-phase response manifests as reoccurrence of diffuse induration and erythema, while in the airways nasal congestion or bronchoconstriction recurs. Many features of the late-phase reaction are similar to those observed in chronic human allergic disease, including: (i) their dependence upon IgE, (ii) the pattern of cellular infiltration

(especially eosinophils, basophils, and Th2 lymphocytes), (iii) the association with reversible airway obstruction and increased airway hyperreactivity (typical characteristics of asthma), (iv) the generation of edema and mucus hypersecretion, and (v) the quantities and types of inflammatory mediators released (e.g., histamine, LTs, cytokines, and chemokines). The late-phase IgE-mediated inflammatory events in humans help to explain how chronic or recurrent allergen exposure leads to enhanced allergen sensitivity ("priming") and the chronic symptoms of allergic rhinitis and asthma.

Local tissue accumulation of eosinophils is prominent in allergic diseases. This is likely due to a combination of factors, including those that mediate preferential eosinophil adhesion (e.g., IL-4, IL-13), via induction of the endothelial adhesion molecule VCAM-1, recognized by the integrin very late-activation antigen-4 (VLA-4) on the eosinophil surface. Preferential migration occurs in response to chemokines (chemotactic cytokines) of the C-C chemo-kine family (such as eotaxins and MCP-4) that are produced by tissue-resident cells such as the respiratory epithelium. Chemokines are recognized by specific receptors. For example, the chemokine receptor CCR3, which selectively binds eotaxins, is prominently and selectively expressed on eosinophils, basophils, and mast cells. Together with cytokines that prolong their survival (e.g., IL-5, granulocyte macrophage colony–stimulating factor [GM-CSF]), eosinophilic inflammatory infiltrates get established. Each of these molecules is thus a possible target for the development of new drugs to treat allergic diseases.

VIII. MEDIATORS OF IMMEDIATE HYPERSENSITIVITY

A. Preformed, granule-based mediators

1. Histamine. Bioactive factors such as histamine are stored within the granules of mast cells and basophils and are essentially fully released within 30 minutes of FcεRI activation. The in vivo administration of histamine reproduces many of the symptoms of acute allergen exposure and, therefore, is the mediator most often identified with immediate hypersensitivity reactions. On the basis of allergen challenge studies, his-tamine released in the acute phase is thought to be of mast cell origin, whereas basophils are responsible for its reappearance in the late phase.

Histamine is produced from histidine by histidine decarboxylase and is packaged with heparin and other proteoglycans in the granule matrix of mast cells. Degradation of histamine occurs rapidly in vivo by two pathways, by either deamination by histaminases or methylation by *N*-methyltransferase. Histamine acts by binding to specific receptor subtypes H1, H2, H3, and H4, the tissue distribution of which determines the character of the response. Given the wide range of biologic responses to allergen, the use of specific histamine receptor antagonists has aided the definition of tissue responses. Histamine binding to H1 receptors is linked to contraction of airway and gastrointestinal smooth muscle, increased vascular permeability, mucus production in the nose, pruritus, and cutaneous vasodilation. H2 receptor activation leads to increased gastric acid secretion, esophageal muscle contraction, vascular permeability and dilation, airway mucus secretion, and pruritus. Furthermore, H2 receptors are on lymphocytes and are mainly inhibitory while promoting $CD8^+$ lymphocyte activity. Also, H2 receptor activation of basophils, eosinophils, and neutrophils suppresses degranulation. H3 receptors are located

in the central and peripheral nervous system, where they act as presynaptic receptors controlling the release of histamine and other neurotransmitters. H4 receptors are thought to be involved in immune regulatory functions, such as chemotaxis and cytokine secretion. High levels of H4 receptor expression are seen in the bone marrow and peripheral hematopoietic cells, neutrophils, eosinophils, T cells, basophils, and mast cells, whereas the spleen, thymus, lung, small intestine, colon, and heart all show moderate expression of H4 receptors.

As previously described, the actions of histamine in the skin lead to the classic wheal-and-flare response; this biologic response is inhibited most effectively by H1 receptor antagonists. Histamine exerts a bronchoconstrictive effect on the smooth muscle of the lower airway, leading to broncho-spasm and wheezing. In addition, edema formation and increased mucous gland secretion are seen in both the lung and nose. Experimental histamine inhalation is used as a measure of bronchial smooth muscle hyperreactivity, a characteristic of asthma. Clinically, antihistamines are effective treatment for allergic rhinitis, but somewhat surprisingly, they show little therapeutic benefit in preventing or mitigating bronchoconstriction in asthma, indicating that the latter is primarily attributable to other mediators.

In the gastrointestinal tract, histamine secretion stimulates both gastric and mucosal cells, leading to increased gastric acid and fluid secretion as well as smooth muscle contraction, resulting in increased peristalsis, hypermotility, and diarrhea.

2. **Neutral proteases and proteoglycans.** Mast cell secretory granules vary in electron microscopic appearance (scrolls, latticed, or grating architecture) as well as in their relative content of neutral serine proteases. These granules are also filled with highly negatively charged proteoglycans such as chondroitin sulfate or heparin that are packaged with the positively charged histamine and neutral proteases. These proteoglycans influence the activity of the proteases by limiting their inactivation as well as slowing the rate of diffusion into the local tissue site. Neutral proteases are the most abundant proteins in mast cell granules and are represented by **chymase, tryptase**, and **carboxypeptidase.**

A. Classification of mast cells by their granule protease content has led to the identification of tryptase-predominant mast cells located in the mucosa of the lung and gastrointestinal tract, with dual chymase- and tryptase-predominant mast cells located in the skin and in submucosal areas. The general actions of these proteases are not well defined but may include digestion of the basement membrane, increased vascular permeability, and activation of proteins involved in wound healing.

The serine protease **tryptase** accounts for up to 20% of all protein produced by the mast cell and can cause bronchial hyperresponsiveness. In animals, tryptase acts as a fibroblast growth factor. It interacts with and activates thrombin as well as the protease-activated receptor-2. In humans, total serum tryptase levels consist of pro–alpha and pro–beta tryptase plus mature beta-tryptase. Pro–beta tryptase, which is secreted constitutively, is the major contributor; hence, pro–beta tryptase levels appear to reflect the total number of mast cells in the body. Baseline levels of protryptase are increased in systemic mastocytosis. Mature tryptases are stored in granules and are released acutely during mast cell degranulation. Thus, mature beta-tryptase levels are helpful in confirming the diagnosis of severe systemic anaphylaxis. There is no direct evidence to support a role for tryptase in

the clinical manifestation of anaphylaxis. The increased serum tryptase levels tend to occur later than the onset of anaphylactic shock (and rash) and well after histamine peaks in the serum. Therefore, the thought is that tryptase itself is not a cause of anaphylactic shock. Tryptase and histamine have also been detected in fluids recovered from allergen-challenged lung, nose, and skin.

The other major mast cell protease, chymase, is prominent in skin and submucosal mast cells and is typically found with carboxypeptidase in the secretory granules. It has been reported to stimulate bronchial mucus secretion in animals and can also cleave vasoactive intestinal peptide (VIP), a mediator of smooth muscle relaxation.

B. Newly synthesized mediators

1. **Leukotrienes.** The arachidonic acid derivatives include members of the LT and prostaglandin families generated through the lipoxygenase and cyclooxygenase (COX) pathways, respectively (Fig. 2-4). LTs collectively represent what was identified in the 1940s as **slow-reacting substance of anaphylaxis (SRS-A)**. Arachidonic acid released from membrane phos-pholipids by phospholipase A_2 (PLA_2) is translocated to the 5-lipoxygenase-activating protein (FLAP) on the nuclear envelope. It is then converted by 5-lipoxygenase (5-LO) to 5-hydroperoxyeicosatetraenoic acid (5-HPETE) and subsequently to leukotriene A_4 (LTA_4). LTA_4 is then converted to dihy-droleukotriene B_4 (LTB_4) by LTA_4 hydrolase or to the cysteinyl leukotriene LTC_4 by LTC_4 synthase. LTC_4 is secreted, and in extracellular locations, it is sequentially converted to LTD_4 and LTE_4 by enzymatic cleavage of glu-tamine and glycine, respectively. The LTs are synthesized and released by various cellular participants in allergic inflammation, including mast cells, basophils, and eosinophils. The levels of LTs in bronchoalveolar and nasal lavage fluids significantly increase minutes after local challenge with relevant allergen in atopic individuals. The **cysteinyl LTs (LTC_4, LTD_4, and LTE_4)** are the most potent known bronchoconstrictors. They also induce mucus secretion, increased vascular permeability, and mucosal swelling. Cysteinyl LTs and LTB_4 are chemotactic for eosinophils and neutrophils, respectively. Other effects of LTs are listed in Table 2-2. The effects of LTs are mediated by two G protein–coupled receptors, CysLT1 and CysLT2, which are localized on various organs including the lungs. CysLT1 receptor antagonists have been shown to inhibit both early- and late-phase pulmonary reactions to allergen challenge as well as exercise-induced airway obstruction. In clinical trials, CysLT1 receptor antagonists also reduced rhinitis symptoms. Similarly, the 5-LO enzyme inhibitor (zileuton) improved pulmonary function as well as reduced asthma and nasal/sinus symptoms in clinical trials.

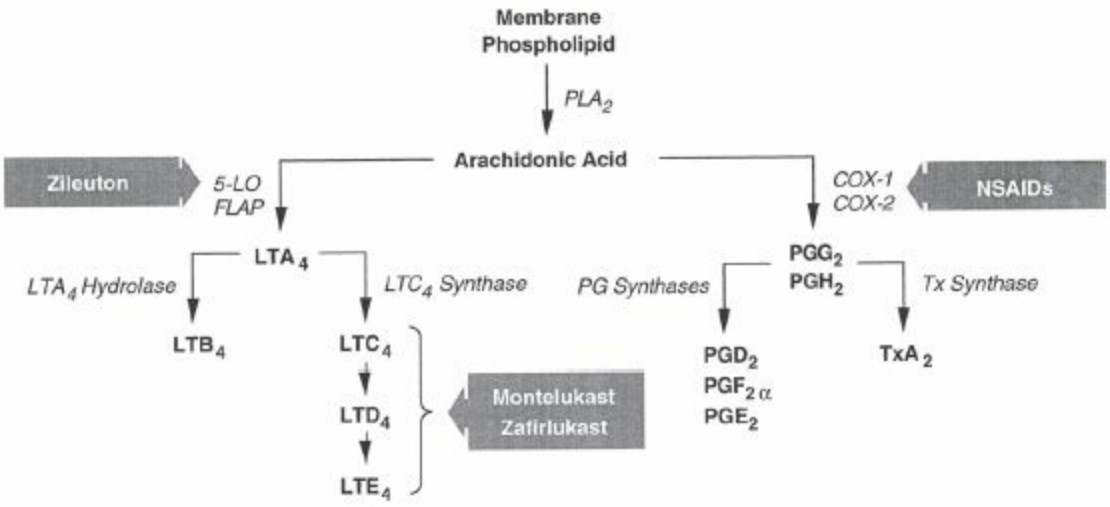

Figure 2-4 Synthesis of leukotrienes and prostaglandins. Various leukotrienes (LTs) and prostaglan-dins (PGs) are generated from free arachidonic acid through the 5-lipoxygenase (5-LO) and cyclo-oxygenase (COX) pathways, respectively. The 5-LO and COX enzymes can be pharmacologically inhibited by zileuton and by nonsteroidal anti-inflammatory drugs (NSAIDs), respectively, whereas effects of the cysteinyl LTs can be inhibited by receptor antagonists such as montelukast and zafirlu-kast. (Reproduced from Adkinson NF, Bochner BS, Busse WW, et al. *Middleton' s allergy: principles and practice*, vol. 1, 7th ed. Philadelphia, PA: Mosby, 2009:320, Figure 19.4, with permission.)

Table 2-2 Major Effects of the Lipoxygenase and Cyclooxygenase Products of Arachidonic Acid Metabolism

Effect	LO- or COX-Derived Mediator
Airway hyperreactivity	LTE_4
Bronchoconstriction	LTC_4, LTD_4, LTE_4, PGD_2, PGF_2, TxA_2
Bronchodilation	PGE_2
Microvascular constriction	$PGF_{2\alpha}$, TxA_2
Microvascular dilation and plasma extravasation	LTC_4, LTD_4, LTE_4, PGD_2, PGE_2, PGI_2
Glandular secretion	LTC_4, LTD_4
Hyperalgesia	PGE_2, PGI_2, LTB_4
Leukocyte chemotaxis and adherence to endothelium	LTB_4, TxA_2, LTD_4
Enhanced platelet aggregation	TxA_2
Suppressed platelet aggregation	PGI_2

LO, lipoxygenase; COX, cyclooxygenase; LT, leukotriene; PG, prostaglandin; Tx, thromboxane

2. **Prostaglandins.** The prostaglandins are generated from arachidonic acid by two forms of COX. COX-1 is constitutively expressed in a wide variety of cell types, whereas COX-2 is highly inducible in mast cells, macrophages, neutrophils, and other cells by proinflammatory factors. During the immediate phase of an allergic reaction, mast cells (but not basophils) release prostaglandin D_2 (PGD_2), which can serve as a marker that distinguishes these cells from basophils. PGD_2 causes bronchoconstriction, with up to a 10-fold greater potency than histamine, as well as vasodilation and resultant nasal

obstruction. A unique PGD(2) receptor, chemoattractant receptor–homologous molecule expressed on T helper (Th)2 cells (CRTH2), which has different functions from the classical PGD(2) receptor, has been identified. Findings suggest that the PGD(2)/ CRTH2 system is stimulatory to Th2 cells, eosinophils, and basophils and is thus important in allergic inflammation. The other prostanoids and their actions are listed in Table 2-2. $PGF_{2\alpha}$ likewise causes broncho-constriction but increases nasal patency because of its vasoconstrictive effect. PGE_2 has been postulated to have a protective role that counterbalances the bronchoconstrictive effects of PGD_2, $PGF_{2\alpha}$, and the cys-teinyl LTs. The production of these prostaglandins is dependent on the presence of the appropriate synthase enzyme in the involved cells.

3. **Platelet-activating factor.** PAF is a proinflammatory phospholipid synthesized and secreted by mast cells, monocytes, and tissue macrophages. Ligation of PAF to its receptor on platelets, monocyte, macrophages, and neutrophils leads to many of the clinical features of anaphylaxis. PAF acetylhydrolase, the enzyme that degrades PAF, is partly responsible for regulating serum PAF levels. A recent study demonstrated that serum PAF levels were directly correlated with the severity of anaphylaxis, whereas serum PAF acetylhydrolase activity was inversely correlated with severity of anaphylaxis. Intradermal injection of PAF in nonallergic subjects causes neutrophil infiltration and plasma extravasation with up to a 1,000-fold greater potency than histamine; in allergic subjects, eosinophil infiltration also occurs. Nasal provocation with PAF causes congestion as well as an influx of eosinophils and neutrophils, whereas its inhalation causes bronchoconstriction that is LT-dependent.

C. Other mediators

1. **Neuropeptides and neurotrophins.** Histamine released during the immediate phase of the allergic reaction can activate sensory nerve fibers in the nasal mucosa, thus inducing the sneezing and secretory reflexes. Such activation can also induce an axon reflex whereby the tachykinins **substance P** and **neurokinin A**, as well as **calcitonin generelated peptide**, are released from nociceptive nerve endings. These neuropeptides can cause vasodilation, increased vascular permeability, bronchoconstriction, and cell migration. **Bradykinin** can also be generated from kininogens during an allergic reaction. This mediator can induce bronchoconstriction, coughing, and plasma extravasation. **Nerve growth factor** is likewise released upon allergen provocation, putatively from epithelial cells, eosinophils, and mast cells. This neurotrophin influences the development of tachykinergic nerve fibers and might thus play a role in the development of hyperreactivity noted in allergic airway disease.
2. **Cytokines.** The exact role of cytokines produced by mast cells and basophils in allergic responses in vivo remains unclear. IgE-dependent activation of cultured human mast cells and tissue-derived mast cells results in the production of a large number of cytokines, including IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-13, and IL-33 as well as GM-CSF, interferon-7 (IFN-7), and tumor necrosis factor-alpha (TNF-α). As with preformed mediators, mast cell cytokine production also appears to be heterogeneous. Activated basophils can synthesize and release sizeable quantities of IL-4 and IL-13, whereas TNF-α is released by mast cells. The relative importance of each of these cytokines can be

inferred based on patterns of release and comparisons to other cellular sources of these products. In particular, the production of IL-4 and IL-13 from these cells may act to amplify allergic inflammatory events. Among the possible effects of these cytokines are enhanced IgE production from B cells, upregulation of the vascular cell adhesion molecule-1 (VCAM-1) on endothelial cells, and the differentiation of Th2 lymphocytes, mucus secretion in the airways (IL-13). Furthermore, release of TNF-α by these cells can have multiple proinflammatory effects, including inducing the transcription factor nfkb that can enhance expression of chemokines, adhesion molecules, and other proinflammatory genes. A limited quantity of preformed TNF-α exists in mast cells. There is also evidence that cultured mast cells or mast cell lines release chemokines such as macrophage inflammatory protein-α (MIP-1α; also basophils), MIP-1β, monocyte chemotactic protein-1 (MCP-1), regulated upon activation, normal T cell expressed and secreted (RANTES), and IL-8, which can act to recruit specific leukocyte subtypes.

IX. APPROACH TO THE PATIENT

As in other medical conditions, a complete history and physical examination is mandatory for the diagnosis and management of patients with allergic disease. The following aspects generally require particular attention:

A. History

1. **Onset of symptoms.** The age at onset of symptoms may suggest whether or not the condition is IgE-mediated. For example, seasonal allergic rhinitis symptoms generally do not develop until 2 to 7 years of age. Food allergy is much more prevalent during infancy and early childhood, although sensitivity could also present or persist later in life.
2. **Character, duration, frequency, and severity of symptoms.** Allergy-related changes may be localized or may involve the respiratory, dermatologic, cardiovascular, and gastrointestinal systems. Respiratory or ocular symptoms may be due to an infectious process if they only last 1 to 2 weeks but are likely related to allergies if they are more persistent. Urticaria has a greater probability of having an allergic etiology if it is acute rather than chronic. The frequency and severity of symptoms may help determine whether to prescribe medications to be used daily or only as needed.
3. **Temporal nature of symptoms.** The allergic condition may be intermittent, year-round, strictly seasonal, or year-round with seasonal exacerbations. Persistent respiratory symptoms during the spring, summer, or fall seasons may indicate sensitivity to tree, grass, or weed allergens, respectively. Year-round symptoms may be attributed to perennial sources of aeroallergens such as dust mites, cockroaches, indoor molds, rodents, or furry pets.
4. **Topologic nature of symptoms.** The patient's disease can be exacerbated at home, in school, or at work. This may indicate sensitivity to allergens or hyperreactivity to irritants that could be present in these places. Of note, cat allergens can be detected in schools even in the absence of these pets, presumably transported there on clothing. About 10% of adult-onset asthma subjects report that their symptoms are worsened by the workplace. Certain patients could have increased work-related risks for sensitivity and exposure to latex, laboratory animals, or biochemical products.

5. **Trigger factors.** Substances in the environment can initiate or exacerbate the patient's symptoms. These can include known sources of aeroallergens as well as nonallergenic elements. Most patients with allergic airway disease develop symptoms upon exposure not only to allergens but also to tobacco smoke and other inhaled irritants. This can be explained by exaggerated mucosal tissue responsiveness to sensory nerve stimulation in the presence of allergic inflammation. Environmental factors such as temperature, humidity, or barometric changes can also affect symptoms of allergic airway disease.
6. **Activity and behavioral factors.** Physical exercise may trigger asthma and, more rarely, anaphylaxis. Outdoor activities may predispose the patient to aeroallergen exposure or to insect stings. Tobacco smoking could significantly worsen allergic airway disease.
7. **Impact of disease on the patient.** Chronic allergic disease can adversely affect the patient's daily activities and performance in school or at work. For example, rhinitis results in more than two million missed school days in the United States annually. Quality of life is an important outcome that needs to be evaluated and monitored as treatment is initiated and continued.
8. **Personal history of atopy.** The occurrence of atopic dermatitis during early childhood increases the probability of subsequent allergic rhinitis and asthma, the so-called "atopic march."
9. **Family history of atopy.** A family history of atopy is a risk factor for allergic diseases such as allergic rhinitis.
10. **Other comorbidities.** The patient can have a disease requiring medications such as beta-blockers that can worsen asthma, cause nasal congestion, or can interfere with the management of anaphylaxis. The presence of hypertension, narrow-angle glaucoma, or urinary retention can preclude the use of decongestants alone or in combination with antihistamines.

B. Physical examination

1. The entire **skin** should be examined for acute and chronic changes, including urticarial lesions, angioedema, dermatitis, and lichenification. The presence of dermatographism (in which the skin becomes raised and inflamed when stroked or scratched) can confound the interpretation of skin test results.
2. The **eyes** should be examined for conjunctival hyperemia and chemosis (edema). Giant papillae >1 mm in size that give a cobblestone appearance to the conjunctivae indicate an allergic rather than an infectious process, although these can also be found in contact lens users. Preauricular adenopathy is absent in allergic conjunctivitis and, if present, suggests viral or bacterial conjunctivitis. Changes in visual acuity also suggest a nonatopic condition. The presence of cataracts that can occasionally be associated with atopic dermatitis and, more rarely, with chronic use of high-dose steroids should be assessed by funduscopy.
3. Examination of the **tympanic membranes** with an otoscope and of the frontal and maxillary **sinuses** by palpation and percussion should be done to check for comorbidities associated with allergic airway disease, such as otitis media and sinusitis, respectively.
4. External examination of the **nose** can reveal a transverse crease resulting from repetitive upward rubbing of the nose, known as the **allergic salute**. The interior of the nose should

be assessed with adequate illumination and exposure using a headlight and nasal speculum or, alternatively, with an otoscope with a large speculum. A more extensive examination of the upper airway can be achieved using a fiberoptic naso-pharyngoscope. The evaluation should note the color of the mucosa, quantity and quality of secretions, and presence and severity of swelling, nasal polyps, ulcerations, and anatomic abnormalities such as septal deviation. If severe swelling is present, topical decongestants can be applied to allow adequate examination.

5. The **oropharynx** should be examined for the presence of erythema, edema, tonsillar hypertrophy, posterior drainage, or oral thrush, the latter being a side effect seen in patients using inhaled corticosteroids.
6. **Chest evaluation.** The chest should be examined by visual inspection for the presence of hyperinflation or use of accessory muscles and by auscultation for adventitious sounds such as wheezing.

C. Clinical and laboratory tests

Certain tests can be performed to confirm or further characterize the allergic condition suggested by the history and physical examination as well as to monitor the progression of disease or its response to treatment. The pretest probability (i.e., the probability of the suspected disorder before the results of the diagnostic test are known) of a positive result should be taken into account in determining whether the test is warranted and in interpreting the results.

PRIMARY TESTS

1. Skin tests

a. Indication. Demonstrating the presence of antigen-specific IgE antibodies is important in establishing the diagnosis of atopic disease and in identifying allergens for which avoidance measures and/or immu-notherapy could be effective. Recognition of a positive skin test by the patient can be useful in gaining cooperation and compliance with these measures. Validated skin testing for immediate hypersensitivity is available for aeroallergens, foods, and insect venoms, as well as for penicillin.

b. General guidelines and methods for skin testing. Scratch tests initially were used to assess sensitivity to allergens, but they have now been replaced by percutaneous (also known as "prick" or "puncture" tests) and intracutaneous (also referred to as "intradermal") skin tests. See **Appendix I** for skin testing methods. In general, skin tests can be followed by specific IgE testing or other *in vitro* tests, when indicated.

(1) Quality control should be applied to ensure the reliability and consistency of the individual tester as well as of the employed devices and allergen extracts. The composition and concentration of allergen extracts should be documented and standardized extracts used whenever possible. The potency of these extracts deteriorates over time, particularly after being diluted and/or exposed to warm temperature. All allergen extracts should be stored at 2°C to 8°C to ensure stability.

(2) Testing with both negative and positive controls needs to be performed to allow proper interpretation of results. Note that wheal formation can occur even with the

diluent (negative) control if the patient has dermatographism, whereas the response to the histamine positive control can be suppressed by certain medications with antihistaminic properties.

(3) Avoid antihistamines to prevent suppression of skin test reactivity. Most first-and second-generation antihistamines should be avoided for at least 72 hours before testing. Hydroxyzine and clemastine should be withheld at least for the preceding 5 days. Cyproheptadine should be withheld for 9 days, and loratadine should be withheld for at least 7 days before testing. Tricyclic antidepressants may also affect the test if taken within the prior 1 to 2 weeks. H2 blockers can cause mild suppression of skin test reactivity if taken <1 day before the test, but this usually is not a problem. Cysteinyl leukotriene antagonists do not suppress skin tests. Short-term use of oral corticosteroids (30 mg of prednisone daily for 1 week) does not affect skin testing, but chronic, high-dose, topical steroid therapy for more than 3 weeks may partially suppress reactivity by reducing the number of tissue mast cells. Therefore, potent topical steroids should be avoided on skin test sites for 2 to 3 weeks before skin testing.

(4) Adverse events: Life-threatening systemic reactions are rarely caused by percutaneous tests. On the other hand, immediate systemic reactions are more common with intracutaneous test. Appropriate emergency equipment and drugs, as well as a physician, should thus be readily available for treatment of a potentially life-threatening reaction. Prescreening with percutaneous tests is a practical way to avoid life-threatening reactions to intracutaneous tests. Skin testing in symptomatic asthmatics should be deferred to avoid even the small risk of further deterioration of lung function.

(5) Selection of allergens: The selection of the number and type of inhalant allergens used for skin testing should be based rationally on their geographic relevance as well as utility in disease management that includes environmental control and/or immunotherapy.

(6) Interpretation of results (see Appendix I for a detailed discussion): When interpreting skin test results, it is important to keep in mind that the clinical significance of such results should be based on their correlation with the patient's history. False-negative results can arise from improper technique, loss of allergen potency, recent anaphylaxis, or drugs that suppress skin reactivity, whereas false-positive results may be caused by skin test materials used at inappropriately high concentrations that induce nonspecific histamine release or local irritation. In general, the sensitivity and negative predictive value of skin tests are higher than their specificity and positive predictive value, respectively. It is important to note that there are large numbers of asymptomatic individuals with allergic sensitization in the general population.

2. **Allergen-specific immunoglobulin E.** Although in vivo skin testing is the preferred method of evaluating IgE-mediated hypersensitivity, *in vitro* measurement of allergen-specific IgE using immunoadsorption methods can be applicable in certain situations. These assays can be useful in cases involving (i) **dermatographism** or generalized dermatitis; (ii) ongoing treatment with

long-acting antihistamines or tricyclic antidepressants that cannot be discontinued; (iii) uncooperative patients; (iv) evaluation of cross-reactivity between insect venoms; (iv) a clinical history suggesting a significant **risk of systemic reaction** to skin tests; (v) **unavailability of reliable skin test reagents** (e.g., latex); and (vi) **postmortem evaluation** of fatal anaphylaxis. Drawbacks of this method include generally lower test sensitivity, higher cost, delay in obtaining results, and lack of a universal consensus in defining what constitutes a positive test. For the assessment of children with food allergy, however, cutoff levels of IgE antibodies with excellent predictive values are available for egg, milk, peanut, fish, soybean, wheat, and tree nuts.

3. **Pulmonary function testing.** Spirometric evaluation of lung function and reversibility of airway obstruction, if present, should be part of the initial assessment of a patient suspected of having asthma. Follow-up pulmonary function tests may also be warranted during return visits to monitor disease progression or response to treatment. Of note, **the perception of asthma severity often does not correlate with the degree of objectively measured airway obstruction.** Routine spirometry provides more information than a peak expiratory flow meter but is less convenient. Neither provides measurements of lung volume or diffusing capacity, which may need to be determined for the evaluation of other diagnostic possibilities. Refer to Chapter 8, **Asthma Diagnosis,** for a more detailed discussion of pulmonary function testing.

SECONDARY TESTS

1. **Provocative tests** that are usually only performed in a research setting can be useful in the clinical evaluation of allergic disease. These techniques should be done only by experienced personnel with the same precautions advised for skin testing regarding the readiness to manage serious reactions. Double-blind, placebo-controlled food challenges can confirm or rule out sensitivity to food in cases where the skin test result does not correlate with the clinical history. This can also help to determine whether a patient previously diagnosed with food allergy during early childhood has outgrown this affliction. Bronchial challenge with a work-related allergen can assist in the diagnosis of occupational asthma. Bronchoprovocation with increasing amounts of a known spasmogen, such as methacholine or hista-mine, to determine the concentration that causes a 20% decrease in forced expiratory volume in 1 second (FEV_1) (PC_{20}), can demonstrate the presence of hyperresponsiveness that is compatible with asthma. Provocative testing is not warranted in cases where the diagnosis is already clearly evidenced by the history and other examinations.
2. A **chest radiograph** can assist in evaluating differential diagnoses as well as the complications of asthma. Chest **computed tomography** (CT) scanning can demonstrate bronchiectasis compatible with allergic bronchopulmonary aspergillosis. **Sinus CT scans** with coronal sections, compared to radiographs, provide greater information regarding the ostiomeatal complex and other structures involved in persistent or recurrent sinus infections.
3. **Serum total immunoglobulin E** levels are of little use in the evaluation of atopic diseases because of their broad and overlapping range across affected and healthy populations. Total IgE levels could be elevated in other clinical conditions such as helminthic parasitic disease,

hyper-IgE syndrome, progressive HIV infection, IgE myeloma, drug-related adverse reactions such as interstitial nephritis, graft versus host disease, and allergic bronchopulmo-nary aspergillosis.

4. Levels of **antigen-specific IgG** to insect venoms produced in response to immunotherapy correlate with protection from reactions to an insect sting (see Chapter 14, **Insect Allergy**). However, other than for experimental purposes, there is no clinical value to measuring IgG to other allergens during or after immunotherapy.
5. The peripheral blood **eosinophil count** can be normal or slightly elevated in patients with atopic disease. However, sustained blood eosinophilia (an absolute eosinophil count >1,500 per μL for months) should initiate a search for nonallergic causes. The eosinophilia can be greater during the pollen season or during asthma exacerbations among susceptible individuals but is typically suppressed among those being treated with steroids or leukotriene modifiers. Similarly, eosinophil counts in nasal or bronchoalveolar lavage fluids, induced sputum, and nasal smears or mucosal scrapings can fluctuate with pollen exposure or medication use. However, these cytologic analyses are not routinely indicated in the assessment of allergic disease.
6. The levels of histamine, leukotrienes, and other **mediators** in biologic fluids obtained in vivo or released *in vitro* correlate with allergic disease and are useful outcomes that are measured particularly for research purposes. Measurement of serum mature beta-tryptase levels, which remain elevated for several hours after being released by mast cells during a systemic allergic reaction, can be clinically indicated in the assessment of possible anaphy-laxis. Although histamine can sometimes also be detected in anaphylaxis, it only remains elevated for about 1 hour. In addition, plasma, rather than serum, should be assayed because unintended artifactual basophil degranulation is more likely to occur in clotted blood. Assays to determine serum levels of total tryptase can also be useful to evaluate the presence of mastocytosis.

CONTROVERSIAL AND UNPROVEN TESTS

Several techniques have been developed for possible application in the diagnosis of allergic disease but are either invalid for any purpose, inapplicable for the evaluation of IgE-mediated sensitivity, or inappropriate for clinical use because of significant inherent limitations. These include so-called cytotoxic testing, provocation–neutralization testing, electrodermal diagnosis, applied kinesiology, the reaginic pulse test, and chemical analysis of body tissues.

Allergen-specific IgG antibody levels are not a marker for allergen sensitization. Rather, they are thought to reflect the extent of an individual's environmental antigen exposure. With regard to diagnostic testing for food allergy, the presence or levels of food-specific IgG or IgG4 antibodies do not correlate with the diagnostic results of positive double-blind placebo-controlled food challenges. Hence, food-specific IgG and IgG4 antibody levels are not useful diagnostic tools for evaluating food allergy or planning food-elimination diets.

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3

Aeroallergens and Environmental Factors

Estelle Levetin, William A. Neaville, Robert Ausdenmoore, and Robert K. Bush

AEROALLERGENS

Aeroallergens are relatively large and complex particles, such as pollen, fungal spores, insect parts, animal dander, plant fragments, and house dust mites, that are capable of eliciting allergic reactions in susceptible persons. These particles contain many molecular components, only some of which are antigenic. When specific antigenic components have been identified, they usually are proteins with carbohydrate sub-units and have a molecular weight of 10,000 to 40,000 D. The **antigenicity** of these molecules is fundamentally a property of their **size**, **spatial configuration**, and **chemical groupings**. The overall **allergic importance** of these particles is not only a function of their **antigenicity** but also of their **availability** in the environment for contact with susceptible persons and the suitability of **particle size** for impingement on the respiratory mucosa.

I. SOURCES AND SIZE OF AEROALLERGENS

A. Biogenic particulate matter commonly identifiable in air samples includes pollen grains and fungal spores. **Unidentifiable biogenic** particulate materials include insect parts, plant fragments, animal dander, and fragmented pollen and fungi. These may be identifiable by immunoassay. **Nonbiogenic** materials, such as hydrocarbons, dirt, salt crystals, or other particulate substances, especially from neighboring farm or industrial activities, may modify allergic responses but are not aeroallergens. **Nonbiogenic**, **nonpar-ticulate** gases such as chlorine, hydrogen sulfide, formaldehyde, gasoline, wood smoke, tobacco smoke, and cooking odors are also not allergens but may influence allergic reactions and act directly as irritants.

B. Most airborne substances of allergic importance identifiable microscopically are between 2 and 60 μm in diameter. Most of these particles (particularly those >15 μm diameter) strike ocular, nasal, and pharyn-geal surfaces because of their linear momentum. Because the majority of allergenic particles do not reach the bronchi, it has been postulated that the bronchial pathophysiologic features in asthma result from a bronchial reflex stimulated by nasopharyngeal receptors. Alternatively, active allergenic material may be eluted from the particles in the nasopharynx and aspirated or may reach the bronchi by a hematogenous route.

II. SAMPLING TECHNIQUES: VOLUMETRIC METHODS

A. Particles heavier than air also exhibit inertial forces, so placing an obstruction in the flow of air causes the particles to impinge on the obstruction. Several sampling techniques take advantage of this fact, but currently these techniques are not recommended because they do not provide volumetric data and significantly underrepresent small particles.

B. With the **rotating arm impactor**, a coated surface is rotated for specific periods of time at a fixed and known speed. Then the particles are counted and expressed as pollen grains or spores

per cubic meter of air. Such methods reduce the factors of wind velocity and direction. One adaptation, the Rotorod Sampler (Fig. 3-1), involves the use of clear acrylic collector rods coated with a thin layer of silicone grease to enhance retention of impacted particles. Other modifications provide **timed intermittent rotation** to prevent overloading and shields to cover exposed surfaces between operating intervals.

Figure 3-1. Rotorod (rotating air impactor) air sampler. (Courtesy Rose Vrtis, University of Wisconsin – Madison.)

C. Inertial suction samplers. When a given volume of air is drawn through membrane filters with defined pore sizes or is aspirated through an orifice with a defined size, particles of a given density leave the air stream and impinge on a collecting surface as the air changes direction because of the impasse. One modification, the **Burkard (Hirst) spore trap** (Fig. 3-2), contains a collecting drum or microscope slide (moving at 2 mm/h) within the trap to allow observations of the diurnal fluctuations in the count. In addition, a rudder vane eliminates the factor of wind direction. Spore traps are the preferred method for sampling particles over a broad particle size range with the resulting samples analyzed by microscopy or other assays. Other suction-type volumetric samplers, for example, Air Sentinal, employ a filter (GORE-TEX) that can be used to collect airborne particles. Immunochemical assay of the collected material can then be used to quantify specific allergens, for example, ragweed allergen, *Amb a* 1.

Figure 3-2. Burkard spore trap volumetric air sampler. (Courtesy Estelle Levetin, University of Tulsa.)

D. Interpretation of sampling data

1. For most sampling procedures, volumetric samples are preferred. Manuals with identification guidelines are available for pollen and mold spores (see Selected Readings). Tabulation of their concentrations (by counting under the microscope) can help determine seasonal prevalence of common aeroallergens in given locales (see Appendix IV). Correlation of particle counts with clinical symptoms on a given day must be cautiously interpreted. There are great variations in the pollen and mold concentrations within any collection period and within any location. Allergic symptoms may be manifested in an individual because of a high peak concentration nearby even if the total daily count is low from a centrally located sampler. Allergen concentrations may be high as those measured by immunoassay in some circumstances, even though the pollen or mold concentration by visual count is low. Unfortunately, some news agencies report daily pollen or mold counts to help promote medication advertisements to a lay public unaware of sampling limitations, the important aspects of personal exposure variations, the effects of multiple sensitivities, or complex allergen dose–response relationships.
2. **Immunochemical quantitation** of allergens in air samples can be made using labeled antibody toward the allergen being measured. Fractions of these allergens can be separated by size by collecting them on filters with progressively smaller pore sizes. Correlations of quantitative data derived by immunochemical means with clinical symptom scores, especially in asthma, are considerably better than the correlation with pollen or mold spore counts. This new, more precise method of quantitating allergen in the air may not only provide better data to correlate with clinical symptoms but also increase the understanding of the effect of antigens not recognizable under the microscope (e.g., dander, fungal fragments, and insect fragments in dwellings and workplaces).

III. POLLEN AEROALLERGENS

Pollen grains are male reproductive structures of seed-bearing plants and function to carry the

male gametes (sperm) to the female gametes (egg), which remain on the plant. Pollen transfer for plants with showy, colorful, and fragrant flowers is accomplished by insects (entomophily). In these instances, the pollen is often large, with an adhesive coating. Remarkable adaptations of some plants allow dissemination of pollen by birds, bats, mice, or even snails.

Most **pollen types of allergic importance are wind-borne** (anemophily). Plants with wind-borne pollen transfers typically have drab, small, inconspicuous, and odorless flowers. Their pollen is usually small, light weight, nonadhe-sive, and produced in enormous numbers.

Most pollen is shed in the morning hours, but dispersal by wind currents may produce maximal pollen concentrations in the afternoon or early evening. Although pollen grains are viable for only a few hours, nonviable pollen is still an active allergen. A gentle wind can carry pollen of anemophilous plants for many miles and produce high pollen concentrations in urban and metropolitan areas, far from their rural or suburban source. A floristic map and regional pollen guide listing the periods of prevalence and relative importance of various pollen in various regions of the United States and Canada appear in Appendix IV.

A. Weeds. Although many different classes of plants may be considered weeds, such as Polygonaceae (buckwheat family), Amaranthaceae (pigweed and waterhemp family), Chenopodiaceae (goose foot family), and Plantaginaceae (plantain family), plants from within the family Asteraceae (Compositae) are most important from an allergy perspective. Within this family, ragweed (*Ambrosia* sp.) is the single most important cause, quantitatively and qualitatively, of seasonal allergic rhinitis (hay fever) in the United States. The highest concentrations of ragweed pollen occur in the central plains and eastern agricultural regions. Cultivation of soil as seen in the Midwestern grain fields allows dense ragweed growth and the greatest seasonal exposure risk for the ragweed pollen–sensitive patient. Ragweed pollen season is typically considered to last 2 to 3 months, with peaks ranging from late August to early October, depending on geographic locale, but climate changes may lengthen these seasons. Peak times for ragweed pollination in the southern United States occur considerably later than in the north. Peak dates occur at the same time for each locale—generally within a 2-week period.

Amb a 1 (formerly termed antigen E) is a highly reactive fraction of ragweed with a molecular weight of 37,800 D, representing approximately 6% of the extractable protein of ragweed. It is 200 times as active as whole ragweed extract. Another fraction, *Amb a 2* (formerly termed antigen K) (molecular weight 38,000 D), is somewhat less potent than *Amb a 1* but still produces reactions in almost all ragweed-sensitive patients.

B. Grasses. It is difficult to distinguish the pollen of different grasses solely on the basis of morphology. Consequently, the importance of individual species is largely determined on the basis of total grass pollen counts combined with a knowledge of the regional presence of individual grass species.

1. In general, **Bermuda grass** is the predominant species throughout the **southern** half of the United States and the **southern Pacific coast regions**. In the **northeastern** and **northern Midwestern states, the bulk of the grass pollen usually comes from the blue grass, orchard grass, timothy grass, and redtop** (see Appendix IV for individual locales).
2. Grass pollen is seen only during the **growing seasons**, so that seasonal patterns (spring and summer) are noted in the north, and more perennial patterns are observed in the south. As with weed pollen, **grass pollen concentrations are generally low at high altitudes,**

such as in the Rocky Mountain area. They are also low in the far north regions of Wisconsin, Michigan, and Maine.

3. Regarding the **frequency** and **severity** of allergic symptoms, grass pollen ranks second only to ragweed in the United States. In other parts of the world, it is the leading aeroallergen.

   Significant cross-sensitivity on skin testing is seen between blue, timothy, orchard, and redtop grasses, but Bermuda grass is antigenically distinct. The extensive cross-reactivity of grass pollen makes skin testing with individual grass extracts unnecessary. Studies indicate that one species of the cross-reactivity grasses is usually sufficient for *in vitro* diagnosis of grass pollen allergy.

C. Trees. The pollen grains of wind-pollinating (anemophilous) trees are the principal causes of respiratory allergy in this botanical group. Insect-pollinating (entomophilous) trees (e.g., ornamental and fruit trees) and some of the anemophilous conifers whose pollen has a thick exine or outer covering (e.g., pine trees) are of minor allergic significance. However, pollen produced from some members of the conifer family Cupressaceae is considered among the most important airborne allergens in many areas.

1. **In general, each tree genus produces pollen morphologically distinct from other genera** and exhibits marked individual variation with respect to the duration, intensity, and seasonal pattern of pollination. However, there are some exceptions. Members of the Cupressaceae family that include junipers, ceders, and cypress all produce pollen that is not distinguishable. These pollen types are identified only as Cupressaceae pollen.
2. **Little cross-antigenicity is noted between genera.** In addition, clustering of certain genera often occurs within the same floristic zone. As a result of these factors, an allergic patient can have selective sensitivity (frequently only to one genus or a few different genera). Pollen from members of the Fagales order are important sources of allergens in spring in the temperate climate zone. *Bet v* 1 from birch pollen is an important allergen from this class and has been extensively studied. There are common cross-sensitizations to food in birch-allergic patients. A well-known example is with raw apple. This is commonly known as the oral allergy syndrome (pollen-food syndrome).
3. In general, the period of pollination within a given locality is relatively short, with the result that tree-sensitive patients often exhibit correspondingly brief periods of discomfort.

Pollination occurs before, during, or shortly after leaves develop in deciduous trees in most species. In more temperate climates, tree pollination concludes by late spring when the trees are fully leaved; in warmer areas, this season may be extended (see Appendix IV). However, it should be noted that some trees produce pollen at other times. There are fall- pollinating species of elm (*Ulmus*) that are commonly used as ornamental. In addition, some species of juniper (*Juniperus*) also pollinate in fall or winter.

IV. FUNGI AS AEROALLERGENS

Fungi belong to a kingdom of multicellular eukaryotes separate from the plant and animal kingdom.

Mold is a term frequently used interchangeably with fungus, but the term fungus is correct, whereas mold more properly refers to amorphous masses of fungi not necessarily of the same type. Despite their simplicity, fungi are among the most successful organisms on earth. They exist in large numbers in almost every environment—dry areas virtually devoid of water or other life, moist areas with wide temperature extremes, in soil, and in fresh water or salt water. Fungi are either saprophytic (obtaining food from dead organic material) or parasitic (feeding on viable tissue).

Fungi are known to be a significant cause of allergic disease. Proteases in fungal extracts have been shown to interact with epithelial cells, leading to production of proinflammatory cytokines, activate eosinophils, and act as Th-2 adjuvants. Several important fungal allergens have been identified. Those most extensively studied include allergens from *Alternaria alternata* (*Alt a* 1), *Cladosporium her-barum* (*Cla h* 1, *Cla h* 2, *Cla h* 3), *Aspergillus fumigatus* (*Asp f* 1), and *Penicillium*. Enolases, which are enzymes required for glycolysis and gluconeogenesis, have been obtained from *Cladosporium*, *Alternaria*, *Saccharomyces cerevisiae*, and *Candida albicans* and have been shown to be highly conserved fungal allergens. With technologic advancements in molecular biology, much has been learned regarding fungal allergenicity. Using molecular biology techniques, fungal allergens have been cloned, which can aid in the standardization of extracts.

A. Structure of fungi. Despite the enormous number of fungal species, only two basic structural forms exist: **Yeast forms** grow as single cells and reproduce by simple division or "budding" to form daughter cells; **hyphal forms** grow as a network of interconnecting tubes. Some hyphae are specialized to produce reproductive spores, which are dispersed by water, wind, insects, or other animals. Most fungi have hyphae, and the vast majority produces spores, which are adapted for airborne dispersal.

B. Classification of fungi. The mode of sexual reproduction has been chosen as the basis for classification of fungi. During the life cycle of most fungal species, reproduction is accomplished by **fragmentation** of the hyphae, or by **production of spores**, or by both processes. Spores may be produced asexually (simple division of a cell) or sexually (fusion of two compatible cells to form a zygote followed by reduction division). Most fungi reproduce both asexually (the **imperfect stage**) and sexually (the **perfect stage**). On the basis of the morphology of their sexual spores, fungi are grouped into three major classes: **Ascomycetes**, **Basidiomycetes**, and **Zygomycetes**. Formerly, a fourth large class was referred to as **Deuteromycetes**, or Fungi Imperfecti, because only asexual spores were identifiable. Subclassifications within this group were based on morphologic differences of spores (form classification); such classification may be expected not to reflect true botanical groupings and probably **does not reflect antigenic similarities** (Table 3-1). The Deuteromycetes included most of the known allergenic fungi. Today, it is known that the majority of these fungi are actual Ascomycetes; for example, *Alternaria*, *Penicillium*, and *Aspergillus* (important allergenic fungi) have been identified as asexual members of the class Ascomycetes. Current classification places the majority of fungi in one of the three main classes.

Table 3-1 Common Fungi and Their Relative Clinical Importance

Ascomycetes

Greater than 60,000 species; prevalent in wood pulp mills, on leaves, bark, deadwood, and soil; locally heavy clouds of ascospores are sometimes seen following rain.

Alternaria: Common fungus identified in air samples, often exceeding pollen counts; saprophytes of leaves, plants, and other decaying organic material; weak plant pathogen; high counts on hot, dry, windy days; indoor concentration reflects outdoor concentration usually by a factor of 25%; major problem for allergic patients, especially in the late summer months.

Aspergillus: Most common indoor fungus in buildings with moisture problems; substrates include dust, carpeting, sheetrock, spoiled food, and other types of organic material; many species are thermotolerant, especially where humidity is high; may colonize the respiratory tract and cause major hypersensitivity problems (allergic bronchopulmonary aspergillosis).

Penicillium: Indoor concentrations often exceed *Aspergillus* concentrations; natural substrate includes spoiled food, cheeses, and multiple types of other organic material; allergic sensitivity to *Penicillium* not predictive of penicillin sensitivity.

Cladosporium (includes *Hormodendrum*): Saprophyte on leaf surfaces, compost and decaying vegetation; typically the most abundant airborne spore type in temperate areas of the world; counts generally far exceeding counts of *Alternaria*; hot, dry, windy days; indoor concentration usually 25% of outdoor concentration; however, *Cladosporium* can colonize indoor substrates as well; major problem in late summer months.

Helminthosporium: Prevalence level generally lower than that for *Alternaria* and *Cladosporium*, but skin reactivity is frequent; especially common in southern states; species of *Bipolaris*, *Drechslera*, and *Exserohilum* are very similar fungi that are often identified as *Helminthosporium*; many species are parasites of crop plants.

Aureobasidium: Found in soil and on leaves but also colonizes lumber and paper; widespread in distribution, but levels usually lower than those of the other prominent outdoor molds; correct name for *Pullularia*.

Basidiomycetes

Greater than 20,000 species; colonize wild and cultivated plants along with many saprophytic species; some of the most conspicuous fungi in the environment including mushrooms, bracket fungi, and puffballs. The spores of these fungi are among the most prevalent fungi identified by stations of the National Allergy Bureau, the American Academy of Allergy, Asthma and Immunology aeroallergen network. Positive skin prick tests to these allergens may be seen in 19% to 30% of individuals tested. Identification of a specific cause and effect relationship between these fungi and clinical allergic situations have not yet been made.

Smuts: High concentrations in contaminated fields of grain; significant respiratory allergen, especially in rural atopic people.

Rusts: Lower concentrations than smuts around contaminated fields, but significant exposure for rural workers, especially in dry, windy situations.

Mushrooms, bracket fungi, and puffballs: Prevalent in damp, forested areas, and lawns especially in wet weather; allergenic importance shown in skin tests and epidemiologic studies.

Zygomycetes

Relatively few species ($N = 250$) are important allergens.

Rhizopus: Prominent in damp interiors; contaminant of bread and sugary foods; moderate allergic importance.

Mucor: Found in damp interiors and soil; contaminant of bread and sugary foods; moderate allergic importance.

Oomycetes

Greater than 250 species identified in air samples; include "downy mildews," which infect grasses and grape or onion crops; spores become airborne in dry, breezy weather; not a proven aeroallergen.

(Modified from Ausdenmoore RW, Lierl MB, Fischer TJ. Inhalant aerobiology and antigens. In: Weiss EB, Stein M, eds. *Bronchial asthma mechanisms and therapeutics*, 3rd ed. Boston, MA: Little, Brown, 1993:552, with permission.)

C. Distribution of fungi. The enormous diversity of these organisms and their remarkable adaptations result in unavoidable human exposure regardless of geographic region. However, because a small amount of moisture and oxygen is a basic requirement for fungal growth, arid regions or areas of high altitude have lower levels of fungi detected by conventional sampling and culture methods. Fungal dormancy is also observed in subfreezing climates. In the northern parts of the United States, fungal spores typically appear as the snow cover disappears, increase as it warms, and peak in the late summer months. In the south, spores can appear year-round with peak concentration in the summer or early fall. Beyond these generalities, **it is difficult to predict fungi prevalence by geographic locale**.

Fungi are also found in indoor environments and can be a source of perennial allergic symptoms.

Spoiled food, soiled upholstery, and garbage containers are favorite substrates for home mold growth. Other common sites include carpeting, damp basements, shower curtains, plumbing fixtures, and contaminated cool-mist vaporizers and console humidifiers. Anytime moisture is available, fungal growth can occur indoors. Plumbing leaks, roof leaks, or other sources of water intrusion can result in serious contamination. Wet sheet rock and ceiling tile are especially prone to contamination by cellulose-degrading fungi.

D. Exposure patterns to fungi. Fungal sensitivity in allergic persons is commonly characterized by sporadic exacerbations that reflect local, concentrated exposures (e.g., visiting a farm, harvesting and storing hay, picking corn, cutting weeds or grass, raking leaves, or hiking in the woods) or periods of maximal fungal growth (e.g., during moist, warm summers and falls, especially with leaves on the ground) (Table 3-1). Over the past two decades, several studies have linked *Alternaria* sensitivity and elevated atmospheric concentrations to asthma severity, asthma exacerbation, or deaths due to respiratory arrest. Although normally found in high airborne levels during extended dry periods in late summer and fall, *Alternaria* sensitivity has also been implicated in thunderstorm asthma. Many occupations predispose workers to a high risk of fungal exposure (e.g., grain farmers, fruit pickers, and paper mill workers). Heavy fungal growth on cut Christmas trees brought indoors can produce a distinctly seasonal pattern in fungal-sensitive patients. Combined with the irritant pine scent and dusty stored decorations, this fungal exposure can initiate allergic symptoms. For general measures toward improving fungal control, see Chapter 4.

E. Assessment of fungal exposure. Empiric fungal-control methods are mandatory for allergic patients to prevent reactions and/or sensitization. In selected situations, identification and semiquantitative determinations of fungal exposures are helpful. These situations include (1) patients with hypersensitivity disease requiring fungal identification for more accurate diagnosis and treatment (e.g., hypersensitivity pneumonitis), (2) monitoring the success of fungal eradication measures, and (3) determining fungal types in locales where prevalence data are unavailable.

Measurement of airborne fungi is accomplished by microscopic identification of samples obtained by volumetric collectors for total spores or for culturable fungi. A variety of instruments are in widespread use for total spore sampling, which is currently the most widely used method. General-purpose mold plates can be made using malt extract, Sabouraud glucose, potato dextrose, corn meal, or V-8 agars. Certain conditions of temperature, humidity, and barometric pressure also can favor growth of molds that are not clinically relevant. Fungal identification requires time, equipment, and mycologic expertise. References are available (see Selected Readings); fungal-identification services are also available at many laboratories throughout the country. Table 3-1 lists important allergenic fungi and their common sources. Individual fungus prevalence by region in the United States can be found in Appendix IV.

V. ANIMAL ALLERGENS

Inhaled dander (epithelial scales) from animal species (other than human) can sensitize an allergic person. Any foreign animal dander could conceivably be responsible for sensitization, but the most common epidermal allergens come from dogs, cats, and hair or feathers (cattle,

horse, sheep, goat, duck) used for stuffing materials. Because the soluble dander, rather than the hair, produces allergic reactions, finished material without dander is less allergenic (e.g., furs used as clothing). Many of the allergens found in the dander are also found in urine and saliva. Studies have characterized the more common allergens. Examples include cat (*Fel d* 1), dog (*Can f* 1, *Can f* 2), and horse (*Equ c* 1, *Equ c* 2).

Sensitivity is often exquisite, especially with cat dander, requiring only a brief or unexpected exposure to create a marked allergic response. The major allergens in cat dander are present on particles that are very small (some <2.5 μm); therefore, they have a low falling rate that causes them to remain airborne for long periods of time even without air disturbance. Clinically, this probably accounts for the sudden onset of symptoms that characterizes encounters with cats or homes with cats. Dander concentrations may be cumulative within a home or other enclosed space; dispersal throughout the home is easily accomplished by the heating system. Vacuuming and pet cleansing are only mildly effective, temporary methods of control. Because the allergen is in the soluble dander, **short-haired breeds or nonshedding dogs** also cause allergy.

Occupational exposure to laboratory animals can be an important cause of difficulty for allergic individuals and can preclude their ability to function in this occupation. It is also possible that large exposures to rodent dander and urine in tenements and other poorly kept dwellings can account for a signifi-cant amount of allergic difficulty. Recent studies have shown that mouse allergen is widely distributed in inner-city homes and may be an important indoor allergen, especially for children with asthma.

VI. HOUSE DUST MITE

Dust from mattress stuffings is an important source of indoor allergens. In 1967, European investigators identified the house dust mite (*Dermatophagoides pteronyssinus*) as a highly allergenic fraction of mattress dust. *Dermatophagoides farinae*, a different species, is the most widespread mite in mattress stuffing samples in North America. House dust mites subsist on human epithelial scales, reaching a seasonal peak concentration in September and October. Secondary reservoirs include overstuffed furniture, rugs, and pillows.

Mite allergenicity does not depend on viability of the mite. Specific mite allergens have been characterized and isolated (*Der p* 1 and *Der p* 2 from *D. pteronyssi-nus*; *Der f* 1 and *Der f* 2 from *D. farinae*). Group 1 (*Der p* 1) and Group 2 (*Der p* 2) allergens are considered the most immunodominant house dust mite allergen. *Der p* 1 has been shown to have cysteine protease activity, which plays a major role in its allergenicity. The proteolytic activity facilitates transepithelial allergen delivery by disruption of tight junctions and also cleaves clusters of differentiation (CD)23 and CD25, which induces immunoglobulin E (IgE) synthesis. *Der p* 2 can induce Th-2 responses via its autoadjuvant properties.

The highest concentrations of mite allergens are found in mite feces; however, some studies have shown that mite allergens can also be carried on a variety of other particles. Therefore, preventive measures include not only destruction of the mite but also physical removal of the mite, or placing a barrier between mite antigen and the susceptible person, or both. Studies have shown that effective mite elimination can be of clinical significance.

Because of the larger size, the falling rate of mite allergen particles is more rapid than that of

cat dander, so exposures to mite particles result in more subtle reactions over a greater period of time. Brief periods of intense mite exposure can occur during vacuuming or other activities that disturb rugs, bedding, or upholstery.

VII. COCKROACHES AND OTHER INSECTS

Allergic persons can show sensitivity by skin testing to a wide variety of insects, suggesting that inhalation of insect parts can play a role in symptom production. The cockroach, in particular, is known to be an important allergen, especially for allergic individuals living in crowded and poorly kept dwellings or working in warehouses or other storage facilities. *Periplaneta americana* and *Blattella germanica* are two species of cockroaches important in atopic diseases. Allergens for both species have been isolated and characterized: *Per a* 1 and *Bla g* 1. Studies have shown cross-reactivity between these species.

Inhalation of insect parts, especially in endemic areas, is suspected as a cause of respiratory disease in atopic individuals. Epidemics of asthma from the caddis fly, moth, mayfly, butterfly, and midge are documented. Absolute proof of this association is lacking because of the inability to identify insect parts microscopically. Current interest in studying the role of insects in allergic disease is increasing with the ability to use immunologic assays on air samples. Sensitivity to the Asian lady beetle (*Harmonia axyridis*) can be a cause of seasonal rhinitis and asthma.

ENVIRONMENTAL FACTORS

I. CLIMATIC FACTORS

It is difficult to isolate and separately study the complex interaction of temperature, humidity, and barometric pressure in producing or exacerbating allergic symptoms. It appears that allergic disease, especially asthma, tends to be adversely affected by **high humidity,** by **sudden temperature changes** (particularly from warm to cold), and by **drops in the barometric pressure.** Intolerance to these factors is highly individual. Dry, cold air commonly precipitates exertional dyspnea.

II. OUTDOOR AIR POLLUTION

A. Industrial smog results from the combustion of liquid or solid fossil fuels and is usually measured by the levels of carbon monoxide, particulate matter, and sulfur dioxide.

1. Carbon monoxide has been linked to certain health problems, including decreased exercise tolerance in ischemic heart disease and atherosclerotic arterial disease in smokers. However, even at peak levels measured in urban rush-hour traffic (120 ppm), it cannot be shown to affect respiratory function adversely in normal persons or asthmatic patients.

2. Particulate matter is made up of several components including silica, metal ions, organic residues, and endotoxins. The inhalable particulate matter is made up of particles <10 mm in diameter (PM 10) or of particles <2.5 mm in diameter (PM 2.5). Inhalable particulate matter can cause coughing and reflex bronchoconstriction and can lead to direct stimulation of small-airway receptors causing bronchiolar constriction. It is also known to potentiate the effect of other pollutants and may act as carriers for other well-described allergens.

Particulate matter has also been associated with increased risk of death from all causes, especially in individuals with cardiovascular and respiratory illnesses. **Diesel exhaust particles (DEPs) are often the major contributors to airborne par-ticulate matter** in major cities around the world. These particles are generally <1 μm in size and, therefore, able to penetrate deep into the lungs. DEPs are well known to shift immune responses toward a Th2 response. They contain polyaromatic hydrocarbons that are converted to quinones and other compounds responsible for marked airway inflammation. Studies have found an adjuvant effect of DEP exposure and pollen exposure. There is also strong evidence from both human and animal studies that DEP exposure causes increases in IgE production. Overall, recent studies have shown that exposure to DEPs in outdoor air can exacerbate asthma and respiratory allergies and may even be factors in developing these conditions.

3. **Sulfur dioxide** does not have a large inflammatory effect at levels found in the atmosphere. However, in very high experimental concentrations, it causes increased airway resistance and suppression of mucosal ciliary activities in humans and other animals. At higher concentrations (from 0.25 to 0.50 ppm), it has been shown to have potent bronchoconstric-tive effects especially noted in those patients with underlying asthma. These effects are typically easily reversed with beta-adrenergic agonists or anticholinergics and do not cause delayed effects.

B. Photochemical smog. Photochemical smog is produced by ultraviolet radiation on hydrocarbons (emitted by automobile exhaust) with the formation of **ozone**, **nitric oxide**, and other **oxidants**. Average urban levels of oxidants may be in the range of 0.2 to 0.5 ppm, with a peak at 1 ppm. Low levels (0.25 ppm) can cause eye irritation and coughing. High concentrations have been associated with diminished vital capacity, forced expiratory volume, and diffusion capacity (even in normal persons). Most of the oxidants measured are ozone (>90%), but nitrogen dioxide is often present in significant concentrations. Nitrogen dioxide, in addition to its direct toxic effect on the lung, may produce irreversible pulmonary changes in smokers. Ozone has been fairly extensively studied, especially in regard to its effect on asthma. Ozone has been found to cause a relatively rapid decrease in forced vital capacity and forced expiratory volume in 1 second. It has also been shown to cause a neutrophil inflammatory response. Some studies have also shown that ozone can potentiate bronchial responsiveness to allergens.

III. INDOOR AIR POLLUTION

Closed ventilation in modern office buildings and homes may increase exposure to common indoor inhalants that are no longer infinitely diluted by out- side air. Passively inhaled tobacco smoke, in particular, is being linked to more respiratory difficulty than previously suspected in coworkers, family members (particularly infants and toddlers), and even house guests. Environmental tobacco smoke has been associated with several increased health risks, including otitis media, upper and lower respiratory tract infections, and wheezing. Environmental tobacco smoke may also help to potentiate atopy through a variety of mechanisms. One possibility includes its effect on increasing the airway mucosal permeability. Another possibility is a direct effect on immune function, including an alteration in monocyte function and a suppression of

functions mediated through gamma interferon, such as phagocytosis of opso-nized antigens.

Aerosols and smoke fumes from kerosene heaters, coal stoves, gas stoves (and pilot lights), fireplaces, and space heaters, plus noxious odors from solvents (e.g., formaldehyde in glues for carpeting and paneling), may all reach higher levels in closed structures. In homes where natural gas is used, another important agent to consider is nitrogen dioxide. Increased levels of nitrogen dioxide have been associated with increased respiratory symptoms. To some extent, this may be due to its role in ozone production.

Many new homes have been constructed in an attempt to conserve energy. Such homes may develop increased relative humidity levels (dampness) because of poor ventilation, the so-called tight-home. Increased rates of respiratory symptoms, including wheezing, have been reported in these dwellings. High concentrations of house dust mite allergens may partly explain this occurrence, but other mechanisms, including fungal sensitivity, require further study.

IV. VIRUSES AND BACTERIA

No proof can be given to support the views of some that true allergic reactions exist toward infectious antigens. It is well known, however, that such infectious agents may frequently trigger and/or complicate allergic reactions (e.g., sinusitis preceding or complicating asthma).

CONCLUSION

Allergic diseases may affect multiple target organs, including nasal mucosa, skin, and the airways, which can lead to significant morbidity. A key feature in the pathogenesis of allergies is inflammation triggered by allergen exposure. With this in mind, the traditional mainstay of treatment has been allergen avoidance. For us to understand the pathogenesis and decrease the morbidity associated with allergic diseases, it is essential that we become familiar with the aeroallergens and environmental factors that can initiate the inflammatory process. The National Allergy Bureau (NAB) of the American Academy of Allergy Asthma and Immunology is a network of 90 air-sampling stations that monitor aeroallergen concentrations. The majority of NAB stations are in the United States with two stations each in Canada and Argentina. Allergen levels from these stations are available online at https://pollen.aaaai.org/nab/. The data from the NAB are valuable for both clinicians and patients to understand allergen exposure.

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4

Rhinitis

Candace Bouler Anz and Mark S. Dykewicz

Rhinitis is one of the most common medical conditions, with allergic rhinitis affecting approximately 10% to 25% of the population in Western societies and around 30 to 60 million patients annually in the United States. While allergic rhinitis is the most common form of chronic rhinitis, 30% to 50% of patients with rhinitis have nonallergic triggers, and around 44% to 87% have mixed rhinitis (a combination of allergic and nonallergic rhinitis). Not only does rhinitis decrease the quality of life, aggravate comorbid conditions, and require significant direct medical expenditures, it also creates even greater indirect costs to society through loss of work and school days, reduced workplace productivity, and decreased school learning. Rhinitis can contribute to sinusitis and is frequently associated with asthma.

I. BACKGROUND AND PATHOPHYSIOLOGY.

Rhinitis is a nasal disorder characterized by rhinorrhea, nasal congestion, nasal pruritus, or sneezing and can be allergic, nonallergic, or mixed (a combination of allergic and nonallergic). Allergic rhinitis is most common, but about 30% to 50% of people with rhinitis have nonallergic forms.

A. Allergic rhinitis occurs when inhaled allergen particles cause sensitization with the production of allergen-specific immunoglobulin E (IgE). Upon subsequent exposure in sensitized individuals, the allergens are recognized by IgE attached to mast cells triggering their degranulation with the release of preformed mediators like histamine and the production of cysteinyl leukotrienes and prosta-glandin D2. These mediators cause acute mucosal edema, mucus secretion, vascular leak, and stimulation of sensory neurons within minutes. A late-phase response also can occur over several hours with the release of chemotactic factors such as IL-5, which results in the influx of inflammatory cells, particularly eosinophils. Although clinical symptoms during the late phase might be clinically similar to those of an immediate reaction, nasal congestion is more prominent.

B. Nonallergic rhinitis is likely caused by a heterogenous group of disorders with a pathogenesis that is incompletely understood, only sometimes involving inflammation.

II. TYPES OF RHINITIS

See Table 4-1.

Table 4-1 Types of Rhinitis

NSAIDs, Nonsteroidal anti-inflammatory drugs.

(Adapted from Wallace DV, Dykewicz MS, Bernstein DI, et al. The Joint Force on Practice Parameters, representing the AAAAI, ACAAI, JCAAI. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol* 2008;122:S1–S84. PMID: 18662584.)

A. Allergic rhinitis has a predominant demonstrable allergic mechanism as discussed above. It can begin at any age, but typical onset is 9 to 11 years. The most common allergic triggers are pollen, fungi, and indoor allergens such as dust mites, pet dander, and cockroaches.

B. Nonallergic rhinitis syndromes

1. **Nonallergic rhinitis without eosinophilia.** Also known as idiopathic rhinitis, nonallergic rhinitis without eosinophilia is characterized by chronic rhinorrhea and/or congestion independent of infection or allergies. Vasomotor rhinitis is a term that sometimes is used synonymously with nonallergic rhinitis without eosinophilia but can have a specific connotation that nasal symptoms are provoked in response to nonallergic environmental factors, such as changes in temperature or relative humidity, odors (e.g., perfumes or cleaning materials), passive tobacco smoke, alcohol, sexual arousal, exercise, and emotional factors. For certain irritant triggers that are relevant to a patient, avoidance can be recommended.
2. **Nonallergic rhinitis with eosinophilia.** NARES is defined as perennial nasal symptoms, typically nasal congestion but also sneezing, rhinorrhea, nasal pruritus, and commonly anosmia, with findings of eosinophilia on nasal cytology in the absence of identifiable allergen sensitivity. This syndrome is usually found in middle-aged adults, and there is some evidence that NARES be an early stage of nasal polyposis and aspirin sensitivity.
3. **Gustatory rhinitis.** Rhinorrhea occurring immediately after food ingestion is a

cholinergic process called gustatory rhinitis. Hot foods and spicy foods are frequently implicated. Individuals may develop nasal congestion after drinking alcoholic beverages due to the pharmacologic ability of ethanol to contribute to nasal vasodilation. IgE-mediated food allergy as a cause of rhinitis symptoms rarely if ever occurs unless accompanied by symptoms involving other organ systems.

4. **Drug-induced rhinitis**. Both topical and oral medications can be implicated in drug-induced rhinitis. Topical vasoconstrictors used for longer than 3 to 5 days may induce rebound nasal symptoms upon discontinuation. This rebound nasal congestion along with decreased mucociliary clearance due to loss of ciliated epithelial cells is termed rhinitis medica-mentosa. Repetitive use of intranasal methamphetamine and cocaine may also produce rebound congestion and septal perforation and erosion. Oral medications responsible for drug-induced rhinitis include nonsteroidal anti-inflammatory agents, oral contraceptives, and antihypertensive medicines such as beta-blockers and angiotensin-converting enzyme inhibitors.
5. **Hormonal rhinitis**. Causes may include the use of oral contraceptives or conjugated estrogens, thyroid disease, acromegaly, puberty, menstruation, lactation, and pregnancy. In pregnancy, hormonal-induced vasodilation and increased blood volume can lead to nasal vascular pooling causing *pregnancy rhinitis de novo*, which is characterized by nasal congestion during pregnancy that typically resolves within 2 weeks of delivery. More commonly observed in pregnancy is the presence of preexisting rhinitis that worsens in about one-third of pregnant women.
6. **Atrophic rhinitis**. Both primary and secondary atrophic rhinitis have been described. The primary form usually occurs in young to middle-aged adults who live in warm climates of developing countries and is commonly associated with sinusitis. The progressive atrophy of the nasal mucosa and resorption of the underlying bone and turbinates defining this condition are proposed to have an infectious basis. Nasal dryness, ozena, which is the presence of foul-smelling nasal crusts associated with a constant bad smell, and abnormally wide-appearing nasal cavities are commonly noted. Nasal biopsy shows squamous metaplasia, glandular cell atrophy, and loss of pseudostratified epithelium. Diminished airflow resistance from nasal mucosal tissue loss paradoxically causes the sensation of severe nasal congestion. Secondary atrophic rhinitis is normally the direct result of trauma, excessive nasal surgery, irradiation, or other primary nasal or sinus conditions.
7. **Occupational rhinitis.** Occupational rhinitis causes symptoms that are temporally related to exposure at work and often improve away from the workplace. This may be triggered by mechanisms that may be IgE mediated (e.g., from laboratory animals, psyllium), immunologic non-IgE mediated (e.g., polyisocyanates in paints), or irritant induced (e.g., chemicals, grain dust). For patients with preexisting nonoccupational rhinitis, exposure to workplace irritants can aggravate symptoms. Allergic occupational rhinitis frequently coexists with occupational asthma. For some but not all exposures, the presence of occupational rhinitis and conjunctivitis may identify patients at greater risk for developing occupational asthma. Occupations more likely to contribute to occupational rhinitis include veterinarians, farmers, livestock workers, food processing

workers, laboratory workers, and assemblers of electronic and telecommunication products.

III. DIFFERENTIAL CONSIDERATIONS

A. Infectious rhinosinusitis. Both acute viral upper respiratory infections (URIs) and acute and chronic bacterial sinusitis can present with symptoms of rhinitis. Constitutional symptoms of fever, myalgias, and malaise in addition to rhinitis, lack of nasal pruritus, and resolution of symptoms within 7 to 10 days is typical of an acute viral URI. Bacterial sinusitis may present with facial pain or pressure, purulent anterior rhinorrhea or postna-sal drip, and persistent or worsening nasal congestion and can be difficult to distinguish from rhinitis based on history alone.

B. Septal deviation can be diagnosed on physical examination by observing external deviation of the nose or by direct visualization with an otoscope. Fiberoptic rhinopharyngoscopy and computed tomographic (CT) scanning can also assist with diagnosis. Septal deviation is commonly asymptomatic but can present with unilateral or bilateral congestion (e.g., when septal deviation has sigmoid configuration).

C. Adenoidal hypertrophy. Usually seen in young children, adenoidal hypertrophy can lead to bilateral nasal obstruction and is associated with nocturnal mouth breathing and snoring. Mirror examination of the nasopharynx, anterior rhinopharyngoscopy, or CT scanning of the nasal airway can facilitate diagnosis.

D. Cleft palate and choanal atresia are structural abnormalities that can cause nasal congestion and obstruction in infants and young children.

E. Nasal polyps. These benign inflammatory growths may cause unilateral or bilateral nasal obstruction, anosmia, and rhinorrhea. Aspirin-exacerbated respiratory disease, formerly referred to as the aspirin triad, is a syndrome in which nasal polyps are associated with asthma and aspirin sensitivity.

F . Concha bullosa, a common anatomic variant, is pneumatization of the middle turbinate and may cause nasal obstruction.

G. Nasal tumors. Tumors of the nasal airway can be benign or malignant and commonly present with obstruction. Juvenile angiofibromas usually occur in adolescent males and present with epistaxis. Nasal carcinoma should be suspected in the elderly who report unilateral epistaxis and nasal pain.

H. Intranasal foreign bodies. The placement of a foreign body such as a small toy part in the nose by a young child can cause to development of unilateral nasal obstruction and foul-smelling, purulent nasal discharge that may lead to sinusitis.

I. Cerebrospinal fluid (CSF) rhinorrhea. The presence of refractory clear rhinorrhea may be a result of CSF leak. While trauma or recent surgery are the most common causes of a CSF leak, this can occur spontaneously. Beta-2-transferrin protein is a sensitive and specific indicator for CSF fluid because it is not found in nasal or ear secretions.

J. Laryngopharyngeal/pharyngonasal reflux. When gastroesophageal reflux involves the upper esophagus, larynx, and/or pharyngeal area, it is often referred to as laryngopharyngeal reflux. Infants with laryngopharyngeal reflux experience frequent choking, apneic spells, recurrent pneumonia (because of concomitant gastroesophageal reflux and/or tracheal aspiration), and

aspiration of formula leading to secondary chemical/infectious rhinitis.

K. Ciliary dysfunction may be primary such as primary ciliary dyskinesia or secondary from a viral infection. Lack of normal functioning cilia can contribute to recurrent rhinitis and sinusitis.

L. Systemic diseases involving the upper airway. Biopsy is required to make many of these diagnoses.

1. **Wegener's granulomatosis**. A systemic necrotizing vasculitis, this may be associated with purulent rhinorrhea and septal erosions and perforations.
2. **Sjögren's syndrome.** This autoimmune disease destroys exocrine glands, which can lead to nasal congestion, dryness, and crusting.
3. **Sarcoidosis.** Characterized by systemic granuloma formation; may present with nasal granulomata and congestion.
4. **Churg-Strauss syndrome**. Also known as allergic granulomatosis and angitis, Churg-Strauss syndrome is an autoimmune vasculitis characterized by chronic rhinosinusitis, asthma, and peripheral blood eosinophilia.
5. **Relapsing polychondritis**. Characterized by deterioration of cartilage; may cause nasal congestion, crusting, rhinorrhea, epistaxis, and hypogeusia. Sustained or recurrent episodes may result in a characteristic saddle nose deformity.
6. **Amyloidosis**. Amyloid deposition in the upper respiratory tract may cause nasal congestion or obstruction.
7. **Midline granuloma.** Typically, a T-cell lymphoma that can cause rhinitis symptoms such as nasal congestion and obstruction.
8. **Granulomatous infections**. Most granulomatous infections (such as TB, mycoses, syphilis) of the upper respiratory tract can cause chronic nasal congestion, recurrent epistaxis, and episodic anosmia.

IV. DIAGNOSIS

In order to appropriately treat allergic rhinitis, it must be distinguished from other forms of rhinitis. This can be done by detailed history, physical exam, and allergy testing if indicated.

A. History

1. **Symptoms**. Allergic rhinitis typically presents with clear rhinorrhea, nasal congestion, sneezing, and pruritus of the nose, eyes, palate, or ears. The presence of nasal pruritus, ocular pruritus, and lacrimation can be indicators that the rhinitis has an allergic rather than nonallergic basis. Many patients will also experience involvement of the mucous membranes of the eustachian tubes, middle ears, and sinuses leading to ear fullness or popping, muffled hearing, facial pressure, and headache. A sore throat and chronic cough may also develop from postnasal drainage. Allergic rhinitis may be accompanied by symptoms of allergic conjunctivitis such as conjunctival injection, chemosis, ocular pruritus, and tearing. This disease complex is called allergic rhinoconjunctivi-tis and is more frequently associated with pollen hypersensitivity. Less ocular symptoms tend to occur with dust mite hypersensitivity. Topical ophthalmic agents can be helpful, and intranasal corticosteroids, oral antihistamines, and intranasal antihistamines have similar effectiveness in relieving ocular symptoms associated with rhinitis. Allergic rhinitis is found in more than 80% of persons with allergic asthma and is a risk factor for future

development of asthma. There is also an association between nonallergic rhinitis and nonallergic asthma. Accordingly, it is recommended that patients with rhinitis should be evaluated for asthma, and patients with rhinitis should be assessed for asthma. A variety of central nervous system (CNS) complaints such as malaise, fatigue, irritability, depression, and anxiety may also occur, commonly peaking with the pollen counts and improving with the conclusion of pollen exposure.

2. **Pattern of symptoms**. It is important to assess the pattern of symptoms when diagnosing allergic rhinitis and also when determining an appropriate treatment. Key considerations would include frequency and seasonality of symptoms. In seasonal allergic rhinitis, symptoms occur during predictable, defined seasons determined by which allergens the patient has become sensitized to. In many regions of the United States, trees pollinate in the spring (February through May), grasses in the late spring and early summer (May and June), and weeds in the late summer and fall (August through October). However, with perennial allergic rhinitis, the sensitizing aeroallergen is present throughout the year. Therefore, a description of seasonal symptoms may lead one to suspect pollen as a trigger whereas perennial symptoms may implicate house dust mites, cockroaches, or animals, although in some regions, pollen can cause perennial symptoms.
3. **Other factors**. One should also assess previous response to medications, the presence of any coexisting conditions, and family history of atopy. A detailed environmental assessment of possible home and work exposures should also be included.

B. Physical examination. Both allergic rhinitis and nonallergic rhinitis can cause infraorbital darkening due to chronic venous pooling known as "allergic shiners" and a horizontal nasal crease in children called an "allergic salute" from frequently rubbing the nose upward in response to nasal pruritus. Mildly injected bilateral conjunctivae with nonpurulent exudate are often visualized on inspection of the eyes in allergic rhinitis. Intranasal exam of the anterior third of the nasal airway can be performed with a handheld scope or a headlamp and nasal speculum. The use of a topical decongestant in the presence of severe mucosal edema can permit greater visualization. Exam in individuals with allergic rhinitis will typically show clear nasal mucus, pale or blue mucosa, and swollen boggy turbinates, whereas nonallergic rhinitis is associated with pale or erythematous mucosa. The exam should inspect the nasal septum to assess if there is significant septal deviation or mucosal erosions and check for nasal polyps or masses. Fiberoptic rhinoscopy permits examination of the posterior and superior nasal airways.

C. Testing

1. **Allergen-specific immunoglobulin E.** The use of immediate skin testing or *in vitro* tests to determine allergen-specific IgE can support or exclude an allergic basis for symptoms. This can assist in selection of pharmacotherapeutic options, some of which are of no value for nonal-lergic rhinitis. In addition, identification of specific allergens responsible for symptoms permits focused allergen avoidance measures and, when appropriate, targeted allergen immunotherapy.

   In order to include all relevant allergens, this testing should be guided by an individual's specific home environment, geographical location, and pattern of symptoms. Immediate skin testing is preferred for its high sensitivity, simplicity, low cost, and rapid

availability of results. However, *in vitro* testing is indicated in the presence of dermatographism, widespread dermatitis, poorly reactive skin tests as seen in some infants and elderly patients, or the inability to withhold medications that may inhibit skin testing such as antihistamines, tricyclic antidepressants, and phenothiazines. It has been proposed that allergic rhinitis may occur due to localized IgE antibody production not associated with positive skin tests or serum-specific tests for IgE, but data are conflicting about its prevalence.

2. **Others.** Although there is lack of consensus about its routine use, nasal cytology may assist in differentiating allergic rhinitis and NARES from other forms of rhinitis by the presence of significant eosinophilia in nasal secretions, whereas significant neutrophilia without eosinophils would suggest bacterial sinusitis or viral URI. Total serum IgE levels or total circulating eosinophil counts are not routinely indicated in the evaluation of rhinitis because neither is sensitive or specific for allergic rhinitis. In evaluation of selected patients presenting with nasal symptoms, special techniques such as fiberoptic nasal endoscopy, inspiratory peak flow measurements, acoustic rhinometry, or rhinomanometry to assess airflow can be useful.

V. TREATMENT

A. Allergen and irritant avoidance measures. Ideally, the management of rhinitis includes identification of these triggers when possible and implementation of avoidance measures when practical.

1. **Outdoor aeroallergens**. For individuals with pollen hypersensitivity, limiting exposure to pollen is achieved by reducing time outdoors during pollen season, keeping windows closed, and using air conditioning.
2. **Indoor aeroallergens**.

a. Dust mites. For house dust mite–sensitive patients, the use of allergen-impermeable pillow and mattress encasings and washing all bedding in water with a temperature >130°F once each week are recommended. Dust mite–allergic children should not sleep with stuffed animals that are reservoirs for dust mites. Available acaricides that kill house dust mites, such as benzoic acid, have been demonstrated to provide only minimal benefit to mite-allergic patients. Vacuuming with conventional vacuum cleaners has not been shown to significantly reduce mite numbers in carpeting and often increases the levels of airborne mite allergen for short periods of time.

b. Pets. When pet hypersensitivity is present, the most important step in allergen avoidance is removal of the animal from the home environment. Once the pet is no longer in the home, elimination of lingering pet dander should be attempted by removing all carpeting and thoroughly cleaning floors, walls, and furniture. However, despite aggressive cleaning, cat allergen can persist for months. In situations where families are reluctant to remove the pet, confining the pet to an uncarpeted room (other than a bedroom) containing a HEPA (High Efficiency Particulate Arresting filter) or electrostatic air purifier may reduce airborne allergen in the remainder of the home by 90%, although improvement in symptoms cannot be assured.

c. Indoor fungi. *Alternaria*, typically an outdoor allergen, has been found to be a

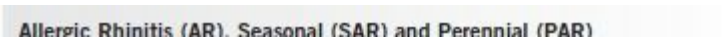
perennial indoor allergen in house dust in certain regions of the country. In homes where water damage has occurred, indoor fungi such as *Aspergillus* and *Penicillium* species can be found. Indoor levels of fungal spores can be reduced by repairing areas damaged by water and eliminating damp spaces that foster mold growth.

d. Cockroaches. Professional extermination, particularly in inner city and rural areas, may be required to eliminate cockroaches in the presence of cockroach hypersensitivity.

e. Medications. Choosing a rhinitis medication should be determined by type of rhinitis, severity, frequency and type of symptom, patient preference for route of administration such as nasal or oral, individual response, and cost. Principal guidelines refer to several terms in making treatment recommendations appropriate for an individual patient. Mild rhinitis is defined to be present when none of the following is present: sleep disturbance; impairment of daily activities, leisure, and/or sport; impairment of school or work; and symptoms present but not troublesome. By ARIA (Allergic Rhinitis in Asthma) guidelines, rhinitis is intermittent if present <4 days per week or <4 weeks duration and considered frequent when these parameters are exceeded. The U.S. Joint Task Force Practice Parameter also uses the term "episodic" environmental rhinitis if symptoms occur sporadically by exposure to aeroallergens not routinely encountered in the patient's environment; treatment strategies can include medication prophylaxis just prior to anticipated allergic environmental exposure or acute treatment once symptoms have developed.

Table 4-2 summarizes considerations about medication selection based upon recommendations of the U.S. Joint Task Force Practice Parameter. Both the U.S. Parameter and ARIA state that an intranasal corticosteroid typically is the most effective medication for allergic rhinitis. For episodic environmental rhinitis or intermittent/infrequent allergic rhinitis, a medication with rapid onset of symptom improvement is preferred. Although some medications can be effective in allergic or nonallergic rhinitis, oral antihistamines, oral antileukotrienes, and nasal cromolyn generally are effective only for allergic rhinitis. Combination therapy may be considered when symptoms are not fully controlled with monotherapy but may not always provide greater effectiveness. Patients receiving intranasal preparations should have their nasal septum periodically examined for the presence of mucosal erosions that may evolve to frank ulcers and nasal septal perforation.

Table 4-2 Medication Options for Rhinitis



Monotherapy	Therapeutic Considerations
Oral agents	
Antihistamines, oral (H1 receptor antagonist)	Continuous use most effective for AR but appropriate for PRN use in episodic environmental or intermittent AR because of relatively rapid onset of action Less effective for nasal congestion Less effective for AR than INSs, with similar effectiveness to INSs for associated ocular symptoms Generally ineffective for non-AR, so other choices favored for mixed rhinitis To avoid sedation (often subjectively unperceived), performance impairment, or anticholinergic effects of first-generation antihistamines, second-generation agents preferred; of these, fexofenadine, loratadine, and desloratadine without sedation at recommended doses
Corticosteroids, oral	A short course (5–7 d) might be appropriate for very severe nasal symptoms. Preferred to single or recurrent administration of intramuscular corticosteroids
Decongestants, oral	Pseudoephedrine reduces nasal congestion Side effects include insomnia, irritability, palpitations, and hypertension
Leukotriene receptor antagonists (LTRAs)	Montelukast is approved for SAR and PAR. Effectiveness of LTRAs and oral antihistamines similar (with loratadine as usual comparator) Because approved for both rhinitis and asthma, can be considered when both conditions present Minimal side effects.
Intranasal agents	
Intranasal antihistamines	Effectiveness for AR equal or superior to oral second-generation antihistamines with clinically significant effect on nasal congestion Generally less effective than INSs Clinically significant rapid onset of action (within several hours or less), making them appropriate for PRN use in patients with episodic AR Because azelastine nasal approved for vasomotor rhinitis, appropriate choice for mixed rhinitis Side effects: somnolence, bitter taste

Intranasal anticholinergic (ipratropium)	Reduces rhinorrhea but not other symptoms of AR Appropriate for episodic environmental AR because of rapid onset of action Minimal side effects, but nasal dryness can occur
Intranasal corticosteroids (INSs)	Most effective monotherapy for AR Effective for all symptoms including congestion Usual onset of action less rapid than oral or intranasal antihistamines, usually within 12 h, can start as early as 3–4 h May consider for episodic environmental AR PRN use (e.g., >50% d use) effective for SAR More effective than combination of oral antihistamine and LTRA Similar effectiveness to oral antihistamines for associated ocular symptoms of AR Appropriate choice for mixed rhinitis because agents in this class also effective for some non-AR Without significant systemic side effects in adults Growth suppression in children with PAR not demonstrated when used at recommended doses Local side effects minimal, but nasal bleeding and rarely nasal septum perforation may occur; advise patients to avoid spraying nasal septum
Intranasal cromolyn	For episodic environmental rhinitis, administration just before allergen exposure protects for 4–8 h against allergic response. Used for maintenance treatment of AR, onset of action within 4–7 d, full benefit can take weeks, less effective than nasal corticosteroids, inadequate data for comparison with leukotriene antagonists and antihistamines Minimal side effects
Intranasal decongestants	Useful for short-term and possibly episodic therapy of nasal congestion, but inappropriate for continued daily use because of risk for rhinitis medicamentosa
Combination therapy	
Antihistamine, oral with decongestant, oral	Provides more effective relief of nasal congestion than antihistamines alone
Antihistamine, oral with LTRA, oral	Might be more effective than monotherapy with an antihistamine or LTRA Combination less effective than INSs Alternative if patients unresponsive to or not compliant with INSs.

Antihistamine, oral with intranasal antihistamine	Combination can be considered, although controlled studies of additive benefit lacking
Antihistamine, oral with INS	Combination can be considered, although supporting studies limited, and many studies unsupportive of additive benefit of adding an antihistamine to an intranasal steroid
Intranasal anticholinergic with INS	Concomitant ipratropium bromide nasal spray with INS more effective for rhinorrhea than administration of either drug alone
Intranasal antihistamine with INS	Combination can be considered based on limited data indicating additive benefit. Inadequate data about optimal interval between administration of the 2 sprays For mixed rhinitis, possible added benefit to combination of intranasal antihistamine with INS
LTRA, oral with INS	Provides subjective additive relief in limited studies; data inadequate
Nonallergic (idiopathic) rhinitis	
Monotherapy	
Oral agents	
Antihistamines, oral (H1 receptor antagonists)	Generally ineffective for non-AR
Decongestants, oral	Pseudoephedrine reduces nasal congestion.
Intranasal agents	
Intranasal antihistamines	Effective for vasomotor rhinitis
Intranasal anticholinergic (ipratropium)	Effective only for rhinorrhea Special role for preventing rhinorrhea of gustatory rhinitis
INSs	Effective for some forms of non-AR, including vasomotor rhinitis and NARES
Combination therapy	Inadequate data to provide firm recommendations in non-AR

AR, allergic rhinitis; INS, intranasal corticosteroids; LTRA, leukotriene receptor antagonist; SAR, seasonal allergic rhinitis; PAR, perennial allergic rhinitis; PRN, as required.

(Adapted from Wallace DV, Dykewicz MS, Bernstein DI, et al. The Joint Force on Practice Parameters, representing the AAAAI, ACAAI, JCAAI. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol* 2008;122:S1–S84. PMID: 18662584.)

f. Allergen immunotherapy/vaccination. Positive long-term disease modification and effective allergic rhinitis symptom control can be achieved with allergen immunotherapy. Patients with allergic rhinitis should be considered candidates for immunotherapy on the basis of the severity of their symptoms, failure or unacceptability of other treatments, comorbid conditions, and possibly as a means of preventing worsening of the condition or the development of comorbid conditions (e.g., asthma and sinusitis).

VI. ALGORITHM FOR ASSESSMENT AND MANAGEMENT OF RHINITIS

See Figure 4-1.

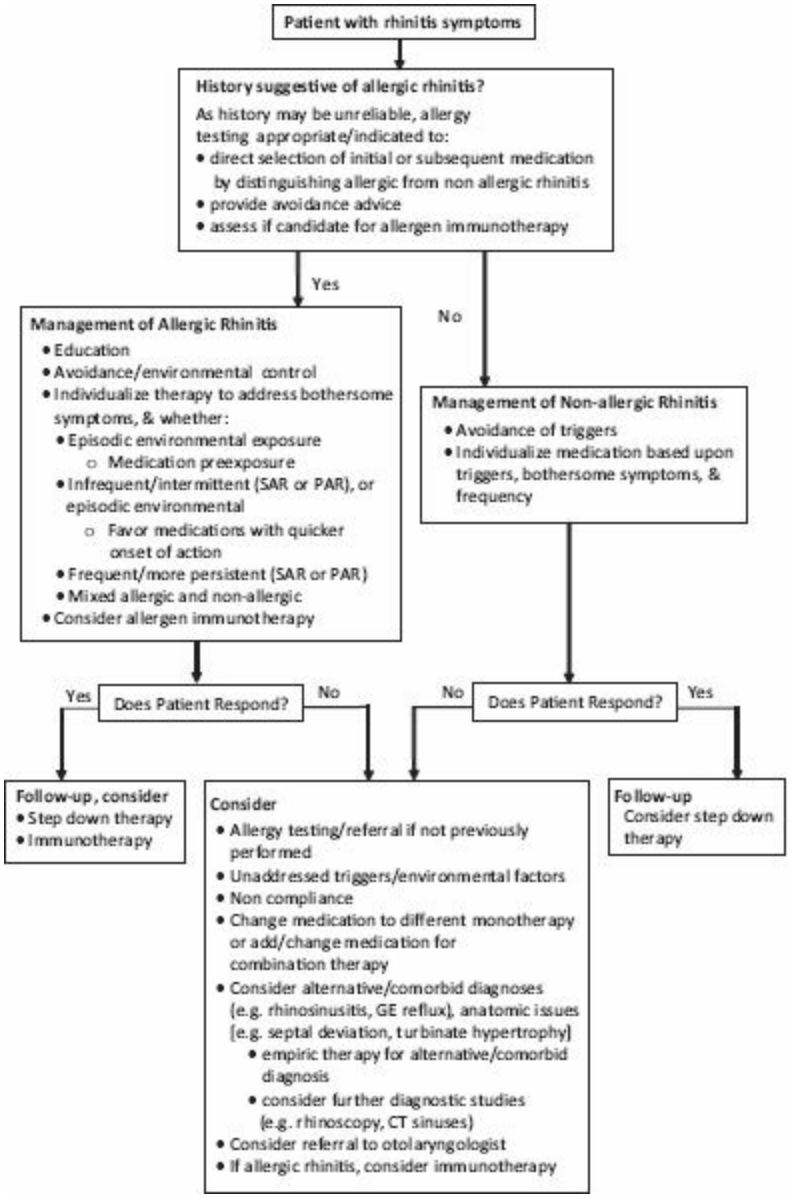


Figure 4-1. Algorithm for assessment and management of rhinitis.

VII. SPECIAL CONSIDERATIONS FOR TREATING RHINITIS IN SELECT POPULATIONS

A. Children. As with most medications, the lowest dose possible to maintain symptom control should be used. Because some, although not all, nasal cor-ticosteroid preparations have been reported to reduce linear growth (at least temporarily), growth should be monitored in children receiving these agents.

B. Elderly. In individuals older than 65 years with perennial rhinitis, allergy is less common than in younger age groups. Rhinitis in the elderly may be caused by types of rhinitis common in other age groups but may also be influenced by age-related physiologic changes, anatomic changes, and medications taken for other medical conditions. Many pathologic changes in connective tissue and vasculature associated with aging may predispose to rhinitis symptoms and often magnify and complicate other causes of rhinitis such as allergic rhinitis. While nasal tissue atrophy may occur in some elderly patients, primary and secondary atrophic rhinitis (discussed earlier) are distinct disorders. Some elderly patients have dryness of the mucus membranes and mucus crusting; treatment options include nasal lavage with isotonic saline and metered nasal sprays with saline/gel moisturizers. Elderly patients are more likely to perceive nasal

congestion in the absence of mucosal edema, underscoring the importance of examining the nasal mucosa in assessment and in making treatment decisions. Medication options for treating rhinitis in more senior patients should be carefully considered in view of comorbidities and adverse effects more likely in this age group. Cholinergically mediated watery rhinorrhea becomes more common in the elderly and can be specifically addressed by the anticholinergic nasal ipratropium bromide, which has a notable safety profile. Because the elderly are more susceptible to adverse systemic anticholinergic and adverse CNS effects of first-generation antihistamines, nonsedating oral antihistamines are preferred. Oral decongestants should be used with caution because of their cardiac, CNS, and bladder function effects.

C. Pregnancy. In addition to pathophysiologic considerations discussed earlier, the selection of medications requires special consideration in pregnancy. Because of concern for potential medication-induced congenital malformation in the first trimester of pregnancy when organogenesis occurs, the FDA risk categories for medications should be taken into account along with human cohort and case–control studies and birth registry data. The most reassuring safety profile in pregnancy is with the use of nasal cromolyn. Cetirizine, chlorpheniramine, loratadine, and tripelennamine may be preferred antihistamines in pregnancy due to their FDA pregnancy category B rating, while other antihistamines are category C. With the exception of intranasal budesonide, which is category B, all intranasal corticosteroids carry a category C rating. Guidelines consider it reasonable to continue any of the intranasal corticosteroids that have adequately controlled the patient's symptoms before pregnancy, but if intranasal corticosteroids are begun during pregnancy, intranasal budesonide may be preferred. Because of the risk of gastroschisis in the newborn, oral decongestants should be avoided during the first trimester. Allergen immunotherapy can be maintained at a stable dose during pregnancy but should not be initiated or escalated.

D. Athletes. Rhinorrhea and chronic or rebound nasal congestion in athletes can affect performance. When treating a competitive athlete, a rhinitis medication should be chosen that will not adversely affect performance and must also be U.S. Olympic Committee and/or International Olympic Committee approved.

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5

Sinusitis, Nasal Polyps, and Otitis Media

Ricardo A. Tan and Jonathan Corren

I. SINUSITIS

A. Definitions and epidemiology

The paranasal sinuses are air-filled cavities that exist within the facial and skull bones that are lined with columnar epithelium and connect to the nasal passages via small openings called ostia. Sinusitis refers to inflammation in the paranasal sinuses, which is most commonly infectious in origin. The infectious etiology can be viral, bacterial, or, less frequently, fungal. Thirty-one million Americans have been estimated to suffer from chronic sinusitis, and patients lose an average of 4 days of work per episode.

Acute sinusitis usually lasts up to 4 weeks, while chronic sinusitis is defined as symptoms persisting beyond 12 weeks. Recurrent acute sinusitis is defined as three or more separate episodes of acute sinusitis per year.

Chronic rhinosinusitis (CRS) is a more recently coined term that reflects the concurrent involvement of both the paranasal sinuses and nasal passages, which is frequently present in many patients with sinus disease. CRS may occur with associated nasal polyps, without nasal polyps, or as a syndrome called "allergic fungal sinusitis."

B. Pathogenesis

1. **Acute sinusitis.** When the ostia of any of the sinuses become obstructed, the environment within the cavity becomes anaerobic, leading to the development of a more acidic pH and retention of mucus. These changes may lead to bacterial growth and infection. Maxillary and ethmoid sinusitis are most common, while the sphenoid sinus is infrequently affected.
2. **Chronic sinusitis.** The sinus tissue and mucus from patients with **CRS without nasal polyps** usually contains a preponderance of eosinophils and neutrophils. The pathophysiology of this form of CRS is poorly understood but may involve some predisposing condition, such as chronic rhinitis (either allergic or nonallergic), an anatomic defect (e.g., septal deviation), or immunodeficiency. In addition, sensitization of Th2 lymphocytes to colonizing fungi (e.g., *Alternaria*) with subsequent eosinophil infiltration has been proposed to play a possible pathogenic role in CRS without nasal polyps.

   In **CRS with nasal polyposis**, there is evidence for local production of specific IgE antibodies against staphylococcal enterotoxins, which act as superantigens and activate large numbers of lymphocytes. Patients with CRS without nasal polyps do not appear to produce these antistaphylococcal enterotoxin IgE antibodies. A role for Th2 fungal sensitization with eosinophilic tissue and mucus infiltration may also contribute to the pathogenesis of CRS with nasal polyps.

   Allergic fungal sinusitis (AFS) represents allergic sinus inflammation caused by fungal colonization and is associated with "allergic mucin." Allergic mucin ranges in color

from light tan to brown to dark green and contains large numbers of degranulating eosinophils and microscopically identifiable fungal hyphae. Allergic mucin is usually not seen during routine physical examination and is most often identified during surgery. Over time, patients with AFS may develop sinus cavity opacification and sometimes local pressure effects on bone. Bony demineralization of the sinus wall may ensue, resulting in expansion of the sinus and possibly mucocele formation. Patients with AFS usually have nasal polyposis, are immunocompetent, and have evidence of fungal-specific IgE by skin tests or IgE immunoassays.

C. Clinical presentation

1. Acute sinusitis. Acute sinusitis most commonly presents as a persistent "cold" that lasts for more than 7 to 10 days. Nasal congestion, sore throat, cough, or postnasal drip may be present during the preceding viral infection but increase in severity as sinusitis develops. Purulent nasal discharge or postnasal drip, headache, facial pressure aggravated by bending over, teeth pain, or pain between the eyes signify that acute bacterial sinusitis may have developed. Low-grade fever and generalized malaise may occasionally be present.

On physical exam, tenderness over the sinuses or over the upper teeth may be noted. Anterior rhinoscopy may show purulent secretions, but their absence does not rule out sinusitis. Fiberoptic rhinoscopy can directly visualize the drainage of pus from the ostia of the sinuses, especially in the middle meatus. Topical decongestants may aid in diagnosis by shrinking the turbinates and allowing the ostia to be visualized.

2. Chronic sinusitis. Patients with chronic sinusitis commonly present with two or more of the following symptoms: nasal obstruction, facial pain or fullness, anterior or posterior drainage, or decreased sense of smell. Chronic sinusitis is less obvious by history and indeed is often missed as symptoms are attributed to other conditions. Occasional patients may also present with only a single long-standing and refractory symptom such as cough, purulent postnasal drip, headache, or halitosis with no other associated symptoms. Facial pain or fullness, if present, is not as intense as in acute sinusitis. Decreased or absent sense of smell is often associated with nasal polyps. In addition to the above symptoms, chronic sinusitis can also cause worsening of asthma.

Physical examination often shows turbinate swelling and erythema, whereas sinus tenderness is rarely found. Purulent discharge may be seen near the sinus ostia or nasal passages, but, as noted in the case of acute sinusitis, its absence does not exclude the diagnosis of chronic sinusitis. Nasal polyps may be present and appear as pale, blue-hued growths often emanating from the area medial to the middle turbinate. Fiberoptic rhinoscopy may be helpful in visualizing polyps or purulent discharge.

D. Diagnostic tests

1. Plain films. Acute sinusitis is usually treated based upon clinical suspicion. However, in occasional patients presenting with atypical symptoms, a Waters' view plain film may be obtained to confirm maxillary or frontal sinusitis. Opacification, air–fluid levels, and moderate-to-severe thickening have all been shown to correlate with positive bacterial cultures taken from the maxillary sinuses in patients with acute sinus symptoms; the most predictive finding is an air–fluid level. Waters' view films may also be useful in young children with atypical chronic symptoms (e.g., chronic cough) to evaluate possible

maxillary sinusitis. When ordering plain films in children, it should be kept in mind that the maxillary and ethmoid sinuses are present on x-rays from birth, while the frontal sinuses cannot be visualized until age 3 to 7 years and the sphenoid sinuses around age 9 years. In general, plain films are insensitive for detecting moderate amounts of mucosal thickening and are very ineffective at imaging the ethmoidal air cells, making it a poor study for patients with suspected chronic sinusitis.

2. **Computed tomography (CT) scan.** The CT scan is considered the gold standard for diagnosing sinus disease. Sinus CTs are most appropriately performed in patients with suspected chronic sinusitis who are still symptomatic despite having received a prolonged trial of medical therapy. A limited-cut, four-slice CT scan of the sinuses is a very cost-effective and adequate alternative to a full CT scan. It can show the ethmoid sinuses in detail and provide some visualization of the osteimeatal complexes in the maxillary sinuses.
3. **Magnetic resonance imaging (MRI).** MRI is especially useful in differentiating inflammatory from neoplastic processes by the signal intensity of their T2-weighted images. Malignant tumors have an intermediate bright signal, while infectious inflammation shows a high signal intensity on T2-weighted images. The main disadvantage of MRI is its limited delineation of bone. Imaging of the ethmoid sinuses is also limited because normal cycles of mucosal swelling cannot be easily distinguished from pathologic swelling. Although the MRI is more sensitive than the CT scan for detecting soft tissue inflammation, the CT scan is sensitive enough for diagnosis in most cases.
4. **Ultrasound.** Sinus ultrasounds are rarely used because of false-positive rates of 39% to 45% and false-negative rates of 42% to 56%. Presently, ultrasound is not considered sensitive enough to substitute for radio-graphic imaging.
5. **Sinus culture.** Cultures of nasal secretions do not accurately reflect sinus microbiology because of frequent bacterial colonization of the nasal passages. Middle meatal aspiration uses a thin plastic tube to aspirate discharge from the ostium in the middle meatus and provides a meaningful culture result. Maxillary sinus punctures are more invasive and no longer commonly done. Sinus cultures are indicated only in complicated (e.g., sinus abscess) and refractory cases with significant systemic symptoms.

E. Microbiology

In acute bacterial sinusitis, the organisms most commonly responsible are *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis*. In chronic sinusitis, *Staphylococcus aureus*, coagulase-negative staphylococci (*S. epidermidis*), Group A streptococcus, *Pseudomonas aeruginosa*, and anaerobic bacteria such as *Fusobacterium* and *Bacteroides* can also be involved. In cystic fibrosis, the most common organism is *P. aeruginosa*.

Invasive fungal sinusitis is most commonly, but not exclusively, seen in immunocompromised patients such as those with chronic diabetes or malignancy or who are receiving chronic treatment with immunosuppressants. *Aspergillus fumigatus* is the most common organism seen regardless of an individual's immune status. *Candida, Sporothrix, Schizophyllum, Mucor, Bipolaris, Alternaria*, and *Curvularia* can also be found. AFS has been shown to be caused by *Aspergillus*, *Bipolaris, Dreschlera*, and *Curvularia* species.

F. Medical therapy

1. **Antibiotic therapy.** Antibiotics are the mainstay of the treatment of acute sinusitis or recurrent acute sinusitis (Table 5-1), as well as infectious exacerbations of chronic sinusitis (Table 5-2). As *S. pneumoniae, H. influenzae*, and *M. catarrhalis* are the most common organisms cultured in all of the above conditions, amoxicillin remains a good first-line choice. Acute sinusitis should be treated for 10 to 14 days and for at least 7 days beyond the first day of marked improvement. For example, if a patient did not feel significantly better until the seventh day of antibiotics, they would receive a total of 14 days of therapy. For patients with significant penicillin allergy, sulfamethoxazole–trimethoprim is an efficacious and cost-effective alternative first-line treatment. In some geographic regions, at least 30% to 40% of *H. influenzae* and 75% to 95% of *M. catarrhalis* produce beta-lactamase. If this is a significant concern, amoxicillin–clavulanate or second-generation cephalosporins (e.g., cefu-roxime) are cost-effective options. In patients with penicillin allergy, macrolides (e.g., clarithromycin) and fluoroquinolones (e.g., levofloxacin, moxifloxacin) are good alternatives.

Table 5-1 Conditions Associated with Sinusitis

Acute and chronic inflammatory conditions
Viral upper respiratory infection
Allergic rhinitis
Nonallergic rhinitis
Nasal polyposis
Anatomic obstructive lesions
Septal deviation
Concha bullosa (aerated middle turbinate)
Enlarged adenoid or tonsils
Foreign body
Dental infection
Systemic diseases
Cystic fibrosis
Wegener's granulomatosis
Primary immune deficiency
AIDS
Immotile cilia syndrome

Table 5-2 Antibiotic Recommendations for Acute Bacterial Sinusitis

First line
Amoxicillin
In cases of penicillin allergy: trimethoprim–sulfamethoxazole, clarithromycin, azithromycin
Second line
Amoxicillin–clavulanate
Second-generation or third-generation cephalosporins
Quinolones

Adult patients with chronic sinusitis and purulent nasal secretions should be treated with 3 to 6 weeks of antibiotics, depending upon the response to treatment, and a good first choice for these patients is amoxicillin–clavulanate or clarithromycin in penicillin-allergic patients. If first-line treatment with either of these medications is not effective, a trial of clindamycin or metronidazole may be useful.If methicillin-resistant *S. aureus* is identified,

the patient's regimen should include clindamycin, trimethoprim–sulfamethoxazole, or linezolid.

2. **Topical and systemic corticosteroids.** Treatment with corticosteroids is most important in patients with chronic sinusitis or in patients who develop acute sinusitis and have concomitant chronic rhinitis. Topical intranasal corticosteroids (INCS) are recommended for at least 3 to 6 weeks in chronic sinusitis. Intranasal mometasone furoate is approved for use in chronic sinusitis at twice the dose given to patients with rhinitis (i.e., 2 sprays per nostril twice daily). In patients with acute sinusitis superimposed upon chronic rhinitis, initiation of treatment with an INCS may be helpful to both conditions. INCS appear to be safe in both chronic and acute sinusitis and do not increase the risk of developing a fulminant infection or complications of infection (e.g., intracranial extension).

   Oral corticosteroids can be used for short periods of time in patients with chronic sinusitis who have severe nasal congestion (e.g., prednisone 15 mg twice daily for 3 to 5 days) and are particularly useful in patients with nasal polyposis (same dose given for 7 to 10 days). In patients with acute sinusitis, severe nasal congestion occasionally prompts the use of oral steroids. However, our own practice would be to first try an intra-nasal decongestant (e.g., oxymetazoline) for 3 days and, if this fails, to consider a short course of oral steroids (prednisone 15 mg twice daily for 3 to 5 days). The presence of fever or systemic toxicity with acute sinusitis would mitigate against the use of oral steroids.

3. **Adjunctive measures.** Adjunctive measures may be helpful in relieving the symptoms of acute and chronic sinusitis. Although data are lacking regarding the efficacy of these measures, clinical experience with some of these interventions is positive.

   Topical and oral decongestants promote drainage of purulent secretions from the sinuses and nose by widening the ostia and shrinking the turbinates. Patients often report relief of facial pressure, ear plugging, and headaches with these agents. Rebound congestion, a common side effect of topical decongestants, can be avoided by limiting the use of these agents to 3 to 5 days.

   Saline irrigation of the nasal passages can help liquefy dried secretions and crusts that may obstruct the nasal airways and sinus ostia. Saline also appears to be a mild natural decongestant. Patients can use a homemade solution by adding a pinch each of salt and baking soda to room temperature water. The saline solution is introduced into the nose with a bulb syringe or other irrigation device and blown out by the patient, and this is performed up to three times per day.

   Guaifenesin is a mucolytic agent and is used to reduce the viscosity of thick secretions. This may be tried if initial efforts with antibiotics, decongestants, and nasal irrigations are slow to work. Other agents occasionally used include astringents (e.g., eucalyptus oil) that may be administered by a facial humidifier for steaming into the nose.

G. Surgical therapy

Patients with chronic sinusitis are occasionally refractory to appropriate medical therapy and continue to have significant and life-changing symptoms. In these patients, sinus surgery may be considered. In addition, patients with acute sinusitis may rarely fail treatment or may present with serious complications, including intracranial extension, brain abscess, or

meningitis. Functional endoscopic sinus surgery (FESS) is the procedure of choice and aims to both remove active infection and improve drainage from the sinuses by removing tissue that is obstructing the sinus ostia. FESS is much less invasive than sinus surgical procedures used in the past.

H. Evaluation of possible predisposing factors

In patients with recurrent acute episodes of sinusitis or chronic sinusitis, potential contributing factors should be considered and evaluated (Table 5-1). The most common underlying condition contributing to both recurrent acute sinusitis and chronic sinusitis is IgE-mediated nasal allergy. In addition to a thorough history that elicits exact symptoms, timing of those symptoms, and perceived triggers of symptoms, a screening allergy skin test or specific IgE panel directed at common local allergens should be obtained.

1. **Immune deficiency.** Humoral immunity should be evaluated in patients with relatively severe recurrent infections accompanied by fever; chronic sinusitis refractory to antibiotics and surgery; or with other recurrent infections (e.g., otitis, bronchitis, pneumonia). This is easily accomplished with a panel of quantitative immunoglobulins (IgG, IgA, IgM) and specific antibodies to *S. pneumoniae*. The most commonly encountered deficiency in humoral immunity is isolated IgA deficiency. Some patients have normal levels of immunoglobulins but very low or absent titers of antibody to *S. pneumoniae*. In these patients, it is important to administer a vaccine to *S. pneumoniae* (Pneumonvax), which should be followed 2 to 4 weeks later with another assessment of *S. pneumoniae* antibodies. The failure to increase these antibodies may provide evidence of humoral immune dysfunction (see chapter 19 on Approach to the Patient with Recurrent Infections).
2. **Wegener's granulomatosis.** In adults with chronic sinusitis, presence of a highly inflamed septal perforation, systemic symptoms (e.g., fever, malaise, fatigue), or associated chronic renal or lung disease should cause a physician to consider Wegener's granulomatosis as a possible diagnosis. While an antinuclear cytoplasmic antibody test is a reasonable and convenient screening test, there are significant numbers of false positives and false negatives, and ultimately, a biopsy of tissue from an involved site may be required to confirm the diagnosis.
3. **Cystic fibrosis**. Cystic fibrosis should be considered in the following presenting with chronic sinusitis: chronic or recurrent diarrhea or failure to thrive; the presence of nasal polyps; other associated recurrent severe infections, including bronchitis, otitis, and pneumonia; or sinus cultures growing *Pseudomonas* species. The most cost-effective screen is a sweat chloride test; genetic tests are more expensive, and screening genetic tests may only pick up 70% of the potential cystic fibrosis mutations.

II. NASAL POLYPS

A. Definitions and epidemiology

Nasal polyps are benign inflammatory masses that originate in the paranasal sinuses and cause blockage of the nasal passages. The majority of patients with nasal polyps have no evidence or history of allergy. As noted above, nasal polyps are present in up to 40% of patients with

cystic fibrosis and are rare in children without cystic fibrosis. In adults, nasal polyps are often associated with aspirin sensitivity and asthma, a syndrome referred to as aspirin-exacerbated respiratory disease and formerly known as Samter Triad.

B. Pathogenesis

The etiology of nasal polyps is not entirely clear but may relate in part to antistaphylococcal enterotoxin IgE antibodies, as noted above. The polyp surface has pseudostratified respiratory epithelium with significant eosino-philic infiltration, goblet cell hyperplasia, and mucus hypersecretion. Polyps most commonly originate in the ethmoid and maxillary sinuses. Inverted papilloma, a malignant lesion, should be distinguished from nasal polyps.

C. Clinical presentation

The presence of nasal polyps is associated with nasal congestion, which may be severe and bilateral; diminished or loss of sense of smell and taste; clear to yellow rhinorrhea; and occasional severe bouts of sneezing. The degree of nasal obstruction depends on the size and extent of nasal polyposis. In some cases, large nasal polyps may eventually cause destruction of nasal bones with symptoms of proptosis, diplopia, and/or intracranial infections.

Physical examination shows the characteristic grape-like, translucent masses in the nasal passages. Nasal turbinate swelling caused by concomitant allergic or nonallergic rhinitis may impair the visualization of polyps. In these situations, application of topical decongestants may be helpful in revealing polyps that are located in the superior or posterior areas of the nasal airway.

D. Diagnostic tests

Flexible or rigid fiberoptic rhinoscopy is a valuable adjunct to the routine nasal examination in patients with suspected polyposis and can help identify small polyps or polyps in more posterior or superior portions of the nasal passages. Coronal CT scan of the sinuses is the imaging procedure of choice for identifying underlying sinusitis and is also essential in delineating the anatomy of the sinuses prior to surgery. MRI is not generally indicated in the evaluation and diagnosis of nasal polyps.

E. Medical therapy

Oral corticosteroids are the most effective known medical therapy for large, obstructing nasal polyps. As noted above, prednisone, given 15 mg twice daily for 7 to 10 days, is usually effective. INCS are often effective in reducing the size of smaller polyps and are indicated as a long-term maintenance treatment after successful treatment of polyps with oral steroids or following sinus surgery. Direct intrapolyp corticosteroid injections may be temporarily effective but are potentially dangerous to adjacent structures and should only be performed by experienced and skilled practitioners if other measures fail.

Leukotriene inhibitors, intranasal cromolyn, topical diuretics, macrolide antibiotics, and intranasal lysine–acetylsalicylic acid have been shown in studies to have varying efficacy for control of nasal polyps. Finally, aspirin desensitization has proven to be effective in preventing recurrence of polyp growth in patients with aspirin-exacerbated respiratory disease (see Chapters 9 and 15 on Asthma Treatment and Drug Allergy).

F. Surgical therapy

Surgical removal of polyps is indicated if medical therapy is not effective, especially if there are severe obstruction and persistent symptoms of infection. A patient's sense of smell and taste may or may not return after surgery. The recurrence rate after surgery has been reported

to be as high as 60%, and many patients require repeat polypectomies. Postsurgical medical treatment with INCS is very important in helping to prevent recurrence.

G. Evaluation of possible predisposing factors

A significant subgroup of patients with nasal polyposis have concomitant immediate hypersensitivity to airborne allergens, which may contribute to many of the symptoms of polyposis. Children with nasal polyp disease should be evaluated for possible cystic fibrosis with a sweat chloride test.

III. OTITIS MEDIA

A. Definitions and epidemiology

Acute otitis media (AOM) refers to an acute suppurative infection of the middle ear space, which usually lasts for 3 weeks or less. Otitis media with effusion (OME) (previously referred to as "secretory" or "serous" otitis media) represents the presence of middle ear fluid without acute signs of inflammation or illness. OME most often follows an episode of AOM and may last for many months. Recurrent AOM is defined as three or more distinct, well-documented episodes in 6 months or four or more episodes in 12 months. Chronic otitis media (COM) is characterized by tympanic membrane perforation associated with persistent ear infection often despite appropriate antibiotic treatment. COM may be dry or may be associated with drainage. If there is chronic purulent drainage, it is termed chronic suppurative otitis media.

AOM is typically diagnosed in young children and is unusual in adult patients. It occurs in roughly 60% of children by age 1 year and in 80% of children by the age of 3 years. Half of all children have had three or more episodes of AOM by the age of 3 years. The incidence of AOM decreases after 7 years of age. Otitis media with effusion is similarly common, noted in approximately 50% of patients during the first year of life.

Epidemiologic risk factors associated with middle ear disease include male gender, absence of breast-feeding, race (Native Americans > Caucasians > African Americans), overcrowding, air pollution, and cigarette smoking by the mother.

B. Pathogenesis

The two factors that contribute most significantly to otitis media are eustachian tube dysfunction and bacterial proliferation in the nasopharynx. The functions of the eustachian tube include pressure equalization, protection of the middle ear from nasopharyngeal secretions, and mucociliary clearance of the middle ear. The descent of the soft palate improves the patency of the eustachian tube and explains the decrease in AOM by 7 years of age. Eustachian tube obstruction results in the development of negative pressure in the middle ear, which is followed by serum transudation in that space. This sterile effusion may become infected by bacteria refluxing from the nasopharynx into the middle ear and cause AOM. Incomplete eradication of an initial infection, or prolonged underventilation of the middle ear, may ultimately result in OME.

C. Clinical presentation

1. **Acute otitis media (AOM).** AOM typically presents with acute unilateral ear pain and decreased hearing that occurs several days after a viral upper respiratory infection. The symptoms frequently start early in the morning and may be associated with fever, nausea,

vomiting, or diarrhea. Irritability is frequently seen in children. Otoscopy usually reveals a red, thickened, and bulging tympanic membrane. Insufflation of air into the external auditory canal (pneumatic otoscopy) generally demonstrates poor mobility of the drum. It is important that the drum may also appear red in a crying child (owing to increased vascularity of the tympanic membrane) and may lead to an incorrect diagnosis of AOM. Purulent discharge may be present if the tympanic membrane is ruptured.

2. **Otitis media with effusion.** Patients with OME are usually asymptomatic but may have a subtle loss of hearing and sense of ear fullness. There may be a history of recurrent AOM in the past, symptoms of allergic rhinitis, upper respiratory infection, or recent air travel. The eardrum may appear yellow, orange, or blue and is often retracted with poor mobility. However, if middle ear fluid is very thin, mobility may appear normal. Air–fluid levels or bubbles may be seen in the tympanic membrane. Physical findings suggestive of allergic rhinitis, sinusitis, or tonsillar hypertrophy should be sought, because these conditions may play important pathogenic roles in OME.

D. Diagnostic tests

1. **Electroacoustic impedance (tympanometry)** is a convenient, simple procedure and is very accurate at detecting OME, which will show a flat configuration. Middle ear fluid can be confidently ruled out when tympanometry is normal.
2. **Audiometry** is an important test in children older than 18 months of age in determining whether OME has resulted in hearing loss. This test should be employed when middle ear fluid has been present for at least 3 months and before deciding whether ventilation of the middle ear is necessary.
3. **Diagnostic tympanocentesis** with culture of middle ear fluid is indicated in children who are extremely ill with AOM who have not responded to an adequate trial of appropriate medical therapy and those in intensive care nurseries.

E. Microbiology

Viral pathogens, most frequently the respiratory syncytial virus, have been found in about a quarter of middle ear aspirates. The most common bacterial organisms detected in middle ear fluid cultures in both adults and children with AOM and OME are *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* (35%, 23%, and 14%, respectively). The most frequent serotypes of *S. pneumoniae* in AOM are 3, 6A, 6B, 14, 19F, and 23F while *H. influenzae* specimens are usually nontypable. Less frequently, *S. aureus,* alpha streptococcus, and Group A hemolytic streptococcus may be present. *S. aureus* can be seen in chronic suppurative otitis media and post–tympanostomy tube insertion. In very young infants and children in intensive care nurseries, Group B streptococci and gram-negative organisms are very common causes of AOM. Biofilms, which are aggregates of bacteria forming a film over mucosal surfaces, have been found in tympanostomy tubes and cholesteatomas and should be considered in patients with poor response to antibiotics.

F. Medical therapy

1. **Acute otitis media**

   a. Observation. Many cases of AOM, especially in children, resolve without pharmacologic therapy. In Europe, the practice of watchful waiting and withholding antimicrobial therapy is common. In the United States, the American Academy of

Pediatrics (AAP) and American Academy of Family Physicians (AAFP) guidelines state than an observation period may be recommended for children 2 years of age or older depending on the level of diagnostic certainty and the severity of illness. Diagnostic certainty is based upon the acuity of onset and presence of middle ear effusion and inflammation. Severe illness is defined as moderate-to-severe otalgia or temperature >39°C, whereas nonsevere illness is defined as mild otalgia and temperature <39°C. Initial therapy with antibiotics is recommended in patients with high degree of certainty of diagnosis and severe illness.

b. Antibiotics. For initial episodes, amoxicillin is the drug of choice and should be given for 10 to 14 days. For penicillin-allergic patients, trimethoprim–sulfamethoxazole, erythromycin–sulfisoxazole, azithromycin, and clarithromycin are good alternatives. In most cases, symptoms should improve significantly within 2 to 3 days. If a child does not respond to an antibiotic within 48 hours and develops local and systemic signs of toxicity, this may indicate resistance to the selected drug. The most commonly employed treatment option in nonreponsive patients is a change of antimicrobial agent to amoxicillin–clavulanate or a second- or third-generation cephalosporin (e.g., cefdinir, cefpodoxime, cefuroxime) for an additional 10 to 14 days. If the patient appears quite ill, the middle ear fluid can be drained and cultured, and subsequent antibiotics can be identified based upon these results. In cases of a ruptured tympanic membrane, a combination of oral and topical antibiotics is recommended. Topical agents with alcohol or aminoglycosides should be avoided when the tympanic membrane is ruptured as toxicity may ensue. Most ruptured membranes will heal spontaneously.

c. Adjunctive measures. Antihistamine–decongestant combinations and topical nasal corticosteroids have not been proven to be effective in children with AOM. However, these agents may have a beneficial effect upon concomitant allergic rhinitis.

2. Recurrent acute otitis media

a. Prophylactic antibiotics. Antibiotic prophylaxis should be reserved for controlling recurrent AOM, defined as three or more distinct, well-documented episodes in 6 months or four or more episodes in 12 months. **Amoxicillin (20 mg per kg q.d.)** and sulfisoxazole (50 mg per kg q.d.) are used most commonly, and treatment should be con*t*inued through the high-risk upper respiratory infection seasons (late fall to early spring).

b. Pneumococcal vaccine should also be encouraged in all children over the age of 2 years who suffer from recurrent otitis media.

3. Otitis media with effusion

Antibiotics are not indicated for the initial treatment of OME; however, treatment may be indicated for effusions that persist for longer than 3 months (Table 5-3). Persistent OME after therapy for AOM is expected and does not require re-treatment with antimicrobials. If indicated, amoxicillin for 10 to 14 days remains the regimen of choice in OME. More potent antimicrobial agents or longer courses of antibiotics have not been shown to be helpful. Antibiotic therapy for OME should be considered in children with associated sinusitis, or those who have a documented conductive hearing loss, vertigo, tinnitus, structural changes

in the tympanic membrane or middle ear, or in infants who are unable to describe symptoms. Following antibiotic therapy, the effusion must be followed carefully to ensure resolution. Adjunctive measures such as antihistamines, decongestants, and nasal steroids have not been demonstrated to have a clear benefit but continue to be used for symptomatic therapy.

Table 5-3 Antibiotic Recommendations for Chronic Sinusitis

First line
Amoxicillin–clavulanate
Second line
Clindamycin
Quinolones
Metronidazole plus macrolide (clarithromycin, azithromycin) or second- or third-generation cephalosporin

G. Surgical therapy

If medical therapy for recurrent AOM or OME is ineffective or poorly tolerated, a patient should be referred for evaluation by an otolaryngologist. Myringotomy with tube placement is effective in reducing the frequency of acute infections and in decreasing the course of chronic effusions and their associated hearing loss. If tube placements are not effective, or a child has persistent adenoidal infection or enlargement, adenoidectomy with repeat tube placement has been shown to be beneficial in children older than age 4 years. Tonsillectomy has not been shown to provide any additional benefit over adenoidectomy alone.

H. Evaluation of possible predisposing factors

Disorders that involve eustachian tube dysfunction frequently lead to AOM and OME (Table 5-4). The most common of these conditions is allergic rhinitis that is present in 30% to 40% of children with recurrent AOM and OME. Patients with chronic nasal symptoms should undergo allergy testing and be treated maximally with allergen avoidance, pharmacologic therapy, and immunotherapy, if indicated. Other conditions to consider in the evaluation of middle ear disease include primary immune deficiency, chronic sinusitis, immotile cilia syndrome, cleft palate, craniofacial anomalies, Down's syndrome, adenoid and tonsillar hypertrophy, and other nasopharyngeal masses.

Table 5-4 Conditions Associated with Otitis Media

Acute and chronic inflammatory diseases
Viral upper respiratory infection
Allergic rhinitis
Chronic sinusitis
Anatomic obstruction
Enlarged adenoids and tonsils
Craniofacial anomalies
Cleft palate disease
Systemic diseases
Primary immune deficiency
Cystic fibrosis
Immotile cilia syndrome
Down's syndrome

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6

Immunotherapy for Inhalant Allergens

Harold S. Nelson

I. INTRODUCTION

Immunotherapy was first introduced as a treatment for grass pollen–induced "hay fever" in 1911. Beginning out of season, Noon and Freeman injected patients subcutaneously with increasing doses of grass pollen extract. Their reported success led to rapid adoption of this treatment not only for other pollen but also for a range of perennial allergens, such as house dust and animal danders, as well as for fungi. It was half a century following its introduction before adequately controlled studies proved the effectiveness of immunotherapy for hay fever and asthma and for mixes of multiple allergens. Other studies confirmed that the response was limited to the allergen that was being injected. More recent studies have documented the disease-modifying potential of immunotherapy. Controlled studies have proven that the benefits derived from immunotherapy persist for years following discontinuation of an adequate course of treatment. Further, in patients with a single sensitivity, immunotherapy greatly decreases the likelihood of developing addition sensitivities, and in those with only allergic rhinitis it decreases the likelihood of developing asthma. Immunotherapy is widely employed for treating patients with allergic rhinitis and asthma, but there are many patients who would likely benefit but are not receiving it. There are multiple reasons for this underutilization of immunotherapy, but two main ones are the occurrence of adverse reactions that can be severe and the inconvenience of repeated visits to a physician's office over a period of several years. Both of these concerns are being addressed by the development of alternative methods of immunotherapy, both administering currently available allergen extracts by routes other than injection and by modifying the allergen extracts to make them less reactive with immunoglobulin E (IgE) and yet retaining their immunogenicity for the T cells, which is thought to be the important mechanism of improvement.

II. CLINICAL INDICATIONS FOR IMMUNOTHERAPY

Immunotherapy was initially introduced for treatment of allergic rhinitis due to grass, and the definitive proof of efficacy was obtained with ragweed pollen extract in seasonal allergic rhinitis. Subsequently, placebo-controlled studies have demonstrated efficacy with several other pollen and also with house dust mite extract in patients with perennial allergic rhinitis. Immunotherapy was used in patients with bronchial asthma soon after its introduction, but the clinical results were not as consistent as those with allergic rhinitis. However, any question regarding efficacy of immunotherapy for asthma has been dispelled by a series of meta-analyses that include all randomized, controlled trials. The most recent, a Cochrane systematic analysis included 88 clinical trials and concluded that there was a significant improvement in asthma symptom scores (standardized mean difference—0.59). Attempts to treat patients with allergy to peanuts with injection immunotherapy were not successful due to repeated systemic reactions, and it is generally accepted that injection therapy is not indicated for food allergy. Currently, oral and

sublingual approaches to immunotherapy for food allergy are being investigated (see chapter 16 on Allergic and Non-allergic Reactions to Food). Until recently, atopic dermatitis was not considered an indication for immunotherapy; however, two recent studies with house dust mite extract, one by injection and one by the sublingual route, reported favorable results. If these are confirmed, immunotherapy may be considered appropriate for selected patients with atopic dermatitis. Immunotherapy is an accepted treatment for sensitivity to venom on the flying Hymenoptera and imported fire ants (covered in Chapter 14 on Insect Allergy).

Immunotherapy has been demonstrated to be effective in children; generally the same doses are employed as in adults. Previously, it was widely stated that children <6 years of age should not receive immunotherapy. The principal arguments against administration to younger children were that there might be difficulty diagnosing a systemic reaction in a young child and that the injections would be very traumatic to young children. More recently, several studies have been reported in which children as young as 3 years of age were treated with injection immunotherapy without adverse outcomes. These reports, plus the now recognized effect of immunotherapy in reducing new sensitizations and progression from allergic rhinitis to asthma, have led to a more flexible approach to immunotherapy in young children.

III. DISEASE MODIFICATION BY IMMUNOTHERAPY

In addition to improving the course of the allergic condition while it is continued, immunotherapy has been shown to reduce the likelihood of development of new sensitivities in monosensitized patients, to reduce the likelihood of developing asthma in patients who only have allergic rhinitis, and to produce benefit in the clinical condition persisting for years following its discontinuation. All these effects are evidence of a modification in the underlying disease process. In studies of monosensitized children and young adults, immunotherapy administered for three years reduced, at follow-up three years after discontinuation, new sensitization from two-thirds in the controls to one-quarter in the treated subjects. In children who received birch and/or timothy immunotherapy for 3 years, the likelihood of not developing asthma at the end of immunotherapy was 2.52 compared to controls, and it remained 2.48 seven years after immunotherapy was discontinued. In a study of grass-sensitive patients who had responded well after 3 or 4 years of immunotherapy, symptomatic improvement was shown to persist in 70% 4 years after discontinuation of treatment.

IV. ALLERGENS EMPLOYED FOR IMMUNOTHERAPY

A. Standardized extracts

Currently, in the United States, there are a number of allergen extracts that have been standardized by the Food and Drug Administration (FDA). The methods of standardization vary within this group. All standardized extracts are available only in 50% glycerin solutions.

1. Grass pollen extracts

Grass extracts (timothy, orchard, Kentucky blue, red top, perennial rye, meadow fescue, sweet vernal, and Bermuda) have been standardized initially by quantitative intradermal skin testing in highly allergic subjects. Subsequent lots are compared to an FDA standard using *in vitro* methods. The grasses are assigned potencies of 10,000 and/or 100,000 bioequivalent allergy units (BAU), the most potent being used for the formulation of extracts for immunotherapy.

2. Short ragweed pollen extract

Short ragweed extracts are sold using standard nomenclature of weight by volume; however, their content of the major allergen of short ragweed, Amb a 1, that must fall within defined limits is listed on the label in FDA units. The 1:10 w/v short ragweed is also considered to contain 100,000 Allergy Units (AU) per milliliter.

3. Cat extract

Cat extracts may be either hair and dander or pelt. In either case, the content of the major allergen, Fel d 1, must be between 10.0 and 19.9 FDA U/mL. The two extracts differ in that pelt has a higher content of cat serum albumin. Cat extracts are expressed in BAU and available as 5,000 and 10,000 BAU/mL.

4. House dust mite extract

The two house dust mite extracts, *Dermatophagoides pteronyssinus* and *D. farinae,* were initially standardized by quantitative intradermal skin testing, and subsequent lots are compared to the FDA standard by *in vitro* testing. House dust mite potency is expressed as Allergy Units that correspond to BAU and are available in potencies ranging from 3,000 to 30,000 AU/mL.

B. Unstandardized extracts

The potency of unstandardized extracts may be expressed as weight of extracted material divided by volume of extracting fluid (w/v) or by the content of protein in the extract (Protein Nitrogen Units or PNU). Most extracts are available as either aqueous or 50% glycerin solutions. Aqueous solutions are generally recommended for pollen since they are more concentrated and glycerin causes pain on injection in a dose-dependent manner. Cockroach and fungal extracts, on the other hand, contain proteolytic activity that is at least in part inhibited by glycerin. Hence, only glycerinated extracts should be used for these allergens.

Some pollen are also available in the United States in an alum-precipitated formulation. These extracts have been shown to cause fewer systemic reactions than aqueous extracts.

1. Pollen extracts

When the major allergen content of unstandardized pollen extracts has been measured, it has fallen within the range of major allergen content of standardized pollen extracts. Therefore, it is usually recommended that unstandardized pollen extracts be used in approximately the same or up to twice the dose of the standardized pollen extracts.

2. Dog extract

Most commercial dog extracts are of very low potency, making their use for immunotherapy of questionable efficacy. The exception is an acetone-precipitated dog extract from Hollister-Stier Laboratories which has been shown by *in vitro* analysis and skin testing to be roughly 35 times more potent than the average commercial dog extract. This extract is available in a 1:100 w/v concentration, with a known major allergen (Can d 1) content of 140 to 160 μg/mL.

3. Cockroach extract

Only extracts in 50% glycerin have been shown to have significant allergenic activity. A recent assessment of three commercially available German cockroach extracts revealed potencies of 1,738 to 8,570 BAU/ mL suggesting they could be used for immunotherapy, but the doses (in milliliters of concentrate) would have to be considerable greater than those

used for pollen.

4. Fungal extracts

The major allergen content of commercially available fungal extracts has been examined for Alternaria alternata, Aspergillus fumigatus, Penicillium notatus, Epicoccus nigrum, Helminthosporium setivus, and Aureobasidium pullalans. For each of these species, the major allergen content has varied more than 100-fold from one company's product to another. The dose of these extracts required for effective immunotherapy is, for the most part, unknown, so the dose to be used is also unknown. It has been recommended in the Immunotherapy Practice Parameters to use the highest tolerated dose.

C. Standardization of allergen extracts in Europe

There is no authority in Europe similar to the FDA in the United States. Allergen extract companies tend to establish their own internal standard for potency, often based on reactivity of allergic patients to the allergen extract and to a nonspecific agent such as codeine or histamine. Several studies suggest widely varying potency among European allergen extracts sold for the same indication.

D. Standardization by major allergen content

In view of the differing methods of expressing potency used in the United States and in Europe, the only common terminology available for comparing studies worldwide is to express dosing as the micrograms of major allergen administered as a maintenance injection. Major allergen content is usually measured by the use of monoclonal antibodies. One problem is that multiple monoclonal antibodies are employed, and they may differ from one another in their quantitation of a major allergen. Nevertheless, it is the best measure of dosing and potency available at this time.

V. PREPARATION OF AN ALLERGEN EXTRACT FOR INJECTION IMMUNOTHERAPY

In preparation of an extract for immunotherapy, there are three considerations: (1) administration of a dose for each allergen that has been shown to be clinically effective in double-blind placebo-controlled trials or, when such data is not available, the optimal dose by inference from what is known regarding the potency of the extract; (2) attention to cross-allergenicity among the extracts employed so that an excess of one allergenic specificity will not limit dosing for the remainder; and (3) attention to the presence of proteolytic activity in extracts so that susceptible allergens are not degraded by the proteolytic activity in others.

A. Dosing

Due to the large placebo effect regularly encountered in immunotherapy plus the variations in exposure to allergens from season to season and location to location, effective dosing can only be determined by randomized, double-blind, placebo-controlled studies. Effective doses expressed by their major allergen content have been established for all of the standardized extracts: short ragweed, timothy grass, birch, house dust mites, cat, dog, and *Alternaria* (Table 6-1). From this information, it is possible to estimate what the effective dose will be of nonstandardized extracts, providing there is some information regarding their usual content of major allergen and providing there is a reasonable range of variability of potency of the

extracts. This latter constraint probably is true for pollen but not for the fungal extracts that have been tested.

Table 6-1 Effective and Ineffective Maintenance Doses for Injection Immunotherapy

Allergen	Effective Dosing by Major Allergen Content	Less Effective or Ineffective Doses by Major Allergen Content
Short ragweed	4–24 µg Amb a 1	0.6 and 2 µg Amb a 1
Timothy grass	15 and 20 µg Phl p 5	2 µg Phl p 5
Birch	3.28 and 12 µg Bet v 1	Not determined
D. pteronyssinus	7 µg Der p 1	0.7 µg Der p 1
D. farinae	10 µg Der f 1	Not determined
Cat	11–17 µg Fel d 1	0.6 and 3 µg Fel d 1
Dog	15 µg Can d 1	0.6 and 3 µg Can d 1
A. alternata	1.6 µg Alt a 1	Not determined

An example of effective and ineffective dosing is provided by a study of two doses of timothy pollen extract for treatment of seasonal allergic rhinitis due to grass in the United Kingdom. A single pre- and co-seasonal course of the high dose, containing 20 µg of Phl p 5 in the maintenance injection, decreased symptoms by 32% and rescue medication use by 41% compared to placebo. A dose containing 2 µg of Phl p 5 provided reduction in symptoms of only 19% and medication use of 14% compared to placebo.

Dosing recommendations from the most recent update of the Immunotherapy Practice Parameters are provided in Table 6-2. The doses are derived from the range of major allergen content that has been determined in the United States. standardized extracts and the effective doses in major allergen listed in Table 6-1.

Table 6-2 Maintenance Doses of U.S. Standardized Extracts from the Immunotherapy Practice Parameters

Allergen	Extracts Available	Dosing Recommended in Practice Parameters
Short ragweed	1:10 w/v (100,000 AU/mL)	1,000–4,000 AU
Timothy grass	100,000 BAU/mL	1,000–4,000 BAU
Bermuda grass	10,000 BAU/mL	300–1,500 BAU
Cat hair or pelt	5,000 and 10,000 BAU/mL	1,000–4,000 BAU
D. pteronyssinus	3,000, 5,000, 10,000, and 30,000 AU/mL	500–2,000 AU
D. farinae	3,000, 5,000, 10,000, and 30,000 AU/mL	500–2,000 AU
Acetone-precipitated dog extract	1:100 w/v	0.04–0.19 mL 1:100 w/v
Nonstandardized pollen extracts	1:10–1:40 w/v and 10,000–40,000 PNU	0.5 mL 1:100 w/v (aqueous) or 1:200 w/v (50% glycerin)
Cockroach and fungal extracts	1:10–1:40 w/v and 10,000–40,000 PNU	Highest tolerated dose

B. Cross-allergenicity

Cross-allergenicity between two allergens generally follows from their relationship in botanical classifications. Thus, there is little or no cross-aller-genicity between members of different families, there is usually a degree of cross-allergenicity between members of the same tribe or genera, and a high degree of cross-allergenicity exists between members of the same genus. It is important to take this cross-reactivity into account when formulating an extract for treatment. Otherwise, one allergenic specificity may be in much higher concentration than the others and limit the buildup to maintenance dosing. Table 6-3 provides examples of some clinically important cross-reacting allergens. The best strategy is either to

use the member of the group that is locally most important or to make a mixture of the locally important allergens and use it as a single extract.

Table 6-3 Important Cross-Reacting Allergens

Botanical Group	Recommendation
Trees	
Cedar, cypress, juniper, arbor vitae	Use locally most important species
Poplar, aspen, cottonwood	Use locally most important species
Grasses	
Northern pasture grasses (timothy, orchard, Kentucky blue, red top, meadow fescue, perennial rye, sweet vernal)	Use timothy or a mixture of locally important species
Bermuda	Antigenically distinct, use separately if locally important
Bahia and Johnson	Antigenically distinct, use separately if locally important
Weeds	
Ragweeds	Use locally important species (short, giant, false, and western cross-react)
Cocklebur, burweed marsh elder	Use locally most important species
Sages, wormwood, mugworts	Use locally most important species
Russian thistle, kochia, lamb's quarters	Use mixture of Russian thistle and kochia if both locally prevalent
Pigweed, Palmer's amaranth, western water hemp	Use locally most important species
Insects	
D. pteronyssinus and D. farinae	Use mixture if both locally important
German and American cockroach	Use a mixture

C. Mixing extracts

Extracts of all fungi and cockroaches contain proteolytic enzymes that degrade some allergenic proteins present in their own and other extracts. The auto-digestion can be inhibited to some extent by using extracts containing 50% glycerin, and these should be the only formulation used for these allergens. Although 50% glycerin is somewhat protective, it causes pain on injection; a lower concentration, such as 20%, is preferred and may be achieved by adding a diluent. To prevent degradation of some of the allergenic proteins, extracts of pollen, animal danders, and house dust mites should not be combined with cockroach or fungal extracts in a treatment extract.

VI. PRACTICAL CONSIDERATIONS

A. Treatment schedules

Customarily, immunotherapy is initiated with injections once or twice weekly, building up the dose to the projected maintenance. Once a maintenance dose is achieved, or the patient has reached the highest dose they will tolerate without unacceptable local and systemic reactions, the frequency of injections is extended, first to two weeks, then three weeks, and finally monthly. It is a common practice to return to weekly injections during at least the first pollen season on maintenance. An example of a schedule for injections is given in Table 6-4. It should be noted that all patients would not begin with the greatest dilution. Commonly, injections will begin at the 1:1,000 v/v dilution. The greater dilution starting point might be selected for highly allergic individuals who are more prone to having systemic reactions.

Table 6-4 Representative Schedule for Administering Injection Immunotherapy

10,000-Fold Dilution (Vial 5) Silver Cap (mL)	1,000-Fold Dilution (Vial 4) Blue Cap (mL)	100-Fold Dilution (Vial 3) Green Cap (mL)	10-Fold Dilution (Vial 2) Gold Cap (mL)	Maintenance Dilution (Vial 1) Red Cap (mL)
0.05	0.05	0.05	0.05	0.05
0.10	0.10	0.10	0.07	0.07
0.20	0.20	0.20	0.10	0.10
0.40	0.40	0.40	0.15	0.15
			0.25	0.20
			0.35	0.30
			0.50	0.40
				0.50

Alternatives to the conventional schedule are rush and cluster. With a rush schedule, patients receive several injections per day on consecutive days. In the extreme, the complete buildup is achieved in one day. Experience has shown that rush immunotherapy is associated with a high rate of systemic reactions, even when multidrug premedication is administered. Cluster immunotherapy involves giving 2 to 3 injections per day, spaced 30 minutes apart. By spacing the cluster visit to twice weekly, maintenance dosing can be achieved in 8 visits over the course of 4 weeks. Compared to conventional dosing, cluster dosing does not appear to be associated with an increase in local or systemic reactions.

B. Premedication

Premedication with a nonsedating antihistamine, although not a standard practice in the United States, has been shown to reduce both local and systemic reactions to allergen extracts both during an accelerated and during a weekly schedule of injections. If used, it would be most cost-effective during the buildup phase when reactions are more common. Administration of the monoclonal anti-IgE antibody, omalizumab, for 3 months prior to an accelerated course of immunotherapy for either allergic rhinitis or allergic asthma has been shown to reduce systemic reactions, but the cost would limit its use for this purpose to highly selected patients.

C. Modification of treatment schedules

Treatment schedules may require modification due to adverse reactions to the injections, due to the patient missing scheduled doses, or due to the patient starting on a new vial of extract. There are very few studies that have assessed the need for and amount of dosage adjustment under these various circumstances. However, some guidance can be offered:

Systemic reactions: Reduce at least to the last tolerated dose and more for severe reactions.

Missed doses: An empiric but untested schedule of reductions is given in Table 6-5. New treatment vial: Reduce dose by 50%. If there is a change in supplier of extracts, the reduction should be: for standardized extracts reduce 80%, for nonstandardized pollen reduce by 95%, and for cockroach and fungi reduce at least 99% (i.e., two 10-fold dilutions).

Table 6-5 Adjustments for Gaps in Immunotherapy

Buildup phase	
Up to 7 d late	Continue buildup as scheduled
8–13 d late	Repeat previous dose
14–21 d late	Reduce dose 25%
21–28 d late	Reduce dose 50%
Maintenance phase	
2–4 wk late	Reduce dose 75%
>4 wk late	Reduce by one or more dilutions depending on the length of time and how long the patient has been on maintenance

Pollen seasons: Some allergists reduce the dose of immunotherapy during a patient's pollen season. Two large prospective studies showed no increase in the incidence of systemic reactions during the pollen seasons for which the patient was receiving treatment, suggesting that reductions in dose during the pollen seasons are not necessary.

VII. ADVERSE REACTIONS

A. Local reactions

Local reactions occur frequently during the course of immunotherapy. Their size and frequency can be reduced by premedication with antihistamines. Large local reactions have been prospectively monitored in two large studies and did not predict systemic reactions nor did modification of the dose in response to a preceding large local reaction reduce the rate of systemic reactions.

B. Systemic reactions

Systemic reactions, varying from symptoms of rhinitis to fatal cardiore-spiratory arrest, can occur following allergen injections. In two prospective studies of high-dose injection immunotherapy including over 9,000 patients, systemic reactions occurred in 2.1% and 2.9% of patients. Risk factors for a systemic reaction identified by one or both studies were: (1) the buildup phase, (2) female gender, and (3) age 16 to 39 years. Systemic reactions were not increased during patients' pollen seasons, and the incidence was the same in those with asthma as in those with allergic rhinitis. Most severe systemic reactions occur within 30 minutes of injection, and this provides the rationale for the recommendation that patients remain in the physician's office for 30 minutes following treatment. One-quarter to half of systemic reactions occur more than 30 minutes following treatment, but these tend to be less severe. Nevertheless, some allergists choose to provide patients receiving injection immunotherapy with an autoinjector preparation of epinephrine to treat any possible late systemic reactions.

The immunotherapy committee of the American Academy of Allergy, Asthma and Immunology has periodically collected data on fatal systemic reactions to injection immunotherapy. A clear pattern has emerged from this data: 88% of fatal reactions occurred in patients with asthma, and their asthma was generally severe and/or poorly controlled. Other prominent risk factors were first injection from a new vial of extract in 21% and dosing errors in 15%. This suggests that fatal reactions from immunotherapy can be largely avoided by addressing these risk factors. It was shown that patients with asthma who were receiving rush immunotherapy to house dust mites were at increased risk of a bronchoconstrictive reaction if their FEV_1 was <80% of predicted and particularly if it was below 70% of predicted. This has led many allergists to monitor peak flows in asthmatics before giving

them their immunotherapy treatment to detect unsuspected loss of asthma control. Also, preparation of individual treatment sets with at least two forms of identification has been used to reduce the chance of giving the patient the wrong extract. The most recent survey by the Committee revealed no reported fatal reactions in the last year, perhaps reflecting improvement in practices aimed at preventing severe reactions.

VIII. IMMUNOLOGIC MECHANISMS

Great strides have been made in understanding the immunologic mechanisms that lead to the clinical improvement with allergen immunotherapy.

A. Humoral changes

A rise in allergen-specific IgG1 and IgG4 subclasses is regularly observed with clinically effective immunotherapy. However, it has also been observed in some studies in which there was no clinical improvement. An early response to immunotherapy is an increase in allergen-specific IgE levels. This is followed by a gradual decline so that several years after initiation of immunotherapy the IgE levels return to and fall below baseline levels. The timing of this decline in specific-IgE makes it improbable that it is responsible for clinical improvement.

B. Cellular changes

There are two, apparently contradictory, cellular immune responses that have been well established to occur with allergen immunotherapy. The first to be defined was an immune deviation, from a Th2 (IL-4) to a Th1 (interferon-gamma) cytokine response to allergen stimulation. The second was the induction of regulatory T cells secreting both IL-10 and TGF-beta. These regulatory T cells suppressed both Th1 (IL-4) and Th2 (interferongamma) responses while shifting the humoral response towards IgG4 (IL-10) and IgA (TGF-beta). Subsequent studies suggested that the regulatory T-cell response occurs early, but tends to wane with time, when the immune deviation from Th2 to Th1 predominates.

IX. ALTERNATIVE APPROACHES TO IMMUNOTHERAPY

Despite the attractiveness of injection immunotherapy for the treatment of allergic rhinitis and allergic asthma, it is employed in the treatment of only a small percentage of those who might benefit. In part, this is explained by the availability of somewhat effective symptomatic therapy with antihistamines and nasal corticosteroids. However, in part, it is explained by concerns for safety as well as the tedious treatment schedule that is imposed to avoid serious reactions. This has led to attempts to make immunotherapy safer and more convenient. There are two principal approaches, either employing a different route of administration with currently available extracts, or modifications in the extracts to reduce reactivity with IgE while retaining the immunologic effect on T cells. Of these alternative approaches, the only one that appears likely to be employed in the United States within the next few years is sublingual administration of allergen extracts.

A. Sublingual immunotherapy

Sublingual administration of allergen extracts has become increasingly popular in many parts of Europe and is in several countries the preferred method of immunotherapy. Many studies and subsequent meta-analyses have shown that this form of treatment is effective for allergic rhinitis and allergic asthma. While not completely free of danger of systemic reactions, fatal or near-fatal reactions have not yet been reported with sublingual immunotherapy. This allows

this form of treatment to be administered by the patient at home, thus addressing one of the principal objections to injection immunotherapy, that of inconvenience. Sublingual immunotherapy has been shown to offer the same disease-modifying outcomes as injection immunotherapy including: decrease in new sensitizations in monosensitized patients, decrease in the development of asthma in patients with only allergic rhinitis, and persistence of improvement for years after discontinuation of a 3- to 4-year course of treatment. There are few direct comparisons between sublingual and subcutaneous immunotherapy, but indirect evidence suggests that subcutaneous immunotherapy may be somewhat more effective, at least in the first year of treatment. Currently, there are no allergen extracts commercially available in the United States that are approved for sublingual administration. Consequently, there is also no billing code for this form of treatment. Several companies are currently pursuing studies which, if successful, may lead to approval of extracts of grass, ragweed, house dust mite, and cat dander for sublingual administration.

X. CONCLUSIONS

A. Allergen immunotherapy is an effective form of treatment for allergic rhinitis, allergic asthma, and perhaps for atopic dermatitis when there is sensitivity to inhalant allergens.

B. Allergen immunotherapy is disease modifying as shown by the reduction in new sensitizations in monosensitized patients, the reduction in the development of asthma in patients with only allergic rhinitis and especially by the persisting benefit now shown for up to 7 years following cessation of treatment.

C. Double-blind, placebo-controlled studies have clearly defined the doses that will produce the desired clinical benefit, as well as those too low to be effective.

D. In preparing allergen extracts for immunotherapy, attention should be given to cross-allergenicity and allergens containing protease activity.

E. Although safety is a concern with injection immunotherapy, the most severe fatal reactions appear to be largely avoidable by appreciation that they occur largely in those with severe and uncontrolled asthma and with the first injections from new vials and with dosing errors.

F. Alternative approaches to immunotherapy are being explored, both using currently available extracts by alternative routes or by modifying the extracts to reduce reactivity with IgE while retaining immunologic stimulation of T cells. Currently the only alternative route being employed with any frequency is sublingual immunotherapy that offers many of the advantages of injection immunotherapy with greater safety and patient convenience but perhaps somewhat less efficacy.

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7

Allergic and Immunologic Disorders of the Eye

Leonard Bielory

The eye is a frequent site of inflammatory responses induced by local and systemic immunologic hypersensitivity reactions. Inflammatory ocular conditions resulting from immune responses are highly prominent because of the eyes' considerable vascularization and the sensitivity of the vessels in the conjunctiva that are embedded in a transparent medium. The eye and its surrounding tissues are also involved in a variety of other immunologically mediated disorders. When such reactions occur, they are frequently seen by the clinical allergist/immunologist, who is in the position to correlate ocular and systemic findings and to coordinate therapy so as to treat underlying disease (if present), rather than only local eye symptoms.

For the allergist, the ocular surface is the primary domain of the interaction between the eye and the environment and includes the cornea and its support tissue the conjunctiva that also includes the ocular adnexa of the lacrimal gland and the lacrimal drainage system that includes ocular allergy and dry eye syndromes.

For the immunologist, the clinical domain—in addition to the ocular surface—includes the involvement of immunologic active responses from the iris to the optic nerve and the adnexal tissue within the orbit.

I. ANATOMY

A. Cross section of the eye

The eye is constructed of four layers from the mast-cell–rich anterior to the vascular contents of the posterior section of the eye: (1) the anterior portion, consisting of the eyelid, conjunctiva, and the tear fluid layer, is the eye's primary barrier against environmental aeroallergens, chemicals, and infectious agents; (2) the collagenous structures (cornea, episclera, sclera) are commonly involved in "collagen" vascular disorders such as rheumatoid arthritis and damage from chronic ocular allergic conjunctivitis such as atopic keratoconjunctivitis (AKC); (3) the highly vascular uvea including the ciliary body, the site of aqueous humor production, and the choroid are common sites for systemically active immune disorders mediated by circulating immune complexes (e.g., vasculitis) and lymphocyte-mediated disorders (e.g., sarcoid); and (4) the posterior portion composed of the retina and the optic nerve, which are involved in central nervous system disorders (e.g., multiple sclerosis) (Fig. 7-1, Table 7-1).

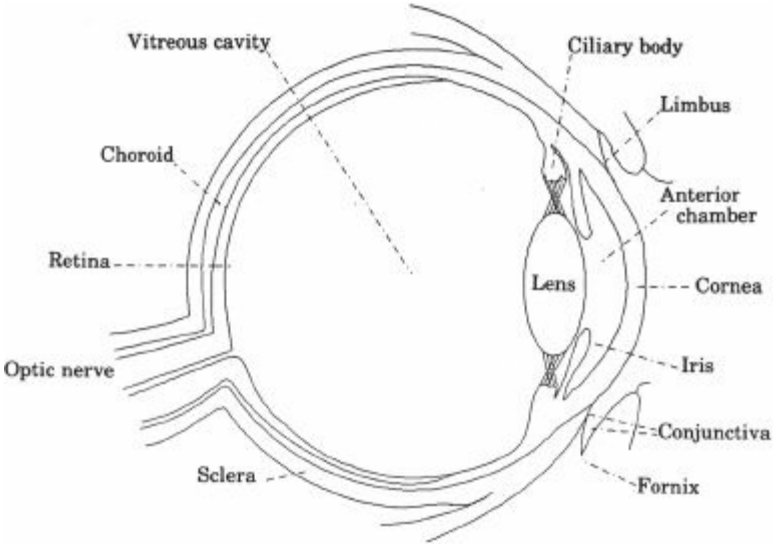

Figure 7-1. Sagittal cross-sectional view of the human eye revealing the parts commonly involved in immunologic hypersensitivity reactions: eyelids (blepharitis and dermatitis), conjunctiva (conjunctivitis), cornea (keratitis), sclera (episcleritis and scleritis), optic nerve (neuritis), iris (iritis), vitreous cavity (vitreitis), choroid (choroiditis), and retina (retinitis). Uveitis involves inflammation of uveal tract (iris, vitreous, and choroid).

Table 7-1 Immunologic Involvement of Various Portion of the Eye

Lids	Blepharitis
	Contact dermatitis
	Discoid lupus
	Chalazion
	Chemical burns
Conjunctiva	Allergic conjunctivitis
	Atopic keratoconjunctivitis
	Vernal conjunctivitis
	Giant papillary conjunctivitis
	Viral conjunctivitis
	Mucocutaneous
	Disorders (pemphigus/pemphigoid, erythema multiforme, toxic epidermal necrolysis)
Sclera	Episcleritis
	Scleritis
Cornea	Corneal allograft rejection
	Amyloid deposition
	Atopic keratoconjunctivitis
	Vernal keratoconjunctivitis
Iris	Iritis
	Cyclitis
	Pars planitis
Vitreous	Vitreitis
	Vasculitis
	Sympathetic ophthalmia
Retina	Retinitis
	Vasculitis
Choroid	Choroiditis
Optic nerve	Optic neuritis
	Vasculitis (e.g., temporal arteritis)
Extraocular muscles	Myasthenia gravis
	Orbital pseudotumor
	Vasculitis
	Grave's ophthalmopathy

II. OCULAR HISTORY AND PHYSICAL EXAMINATION FOR THE ALLERGIST

A. Ocular history

A detailed and accuate history is the most important element in distinguishing allergic from nonallergic causes of conjunctivitis as they commonly reveal recent exposure to individuals with conjunctivitis or upper respiratory tract infections, sexual activity, association with animals that may cause various forms of infectious conjunctivitis, and systemic autoimmune disorders.

1. Age plays a role in the evaluating potential infectious causes. In preschool children, the conjunctivitis–otitis media syndrome occurring frequently is usually caused by nontypeable *Haemophilus influenzae* or *Streptococcus pneumoniae*. In teenagers and adults, a sexual history may suggest a chlamydial or a neisserial infection.
2. Direct questioning of the patient will often reveal the frequent use and abuse of over-the-counter (OTC) medications, such as vasoconstrictors or artificial tears, cosmetics, or contact lens wear, all capable of producing inflammation (conjunctivitis medicamentosa or toxic keratopathy).
3. Knowledge of systemic diseases such as rheumatoid arthritis will heighten the awareness of associated autoimmune-related ocular conditions such as keratoconjunctivitis sicca (KCS) or scleromalacia.
4. As with all allergies, environmental factors and time of onset of symptoms must be addressed, including seasonal variation and exposures (i.e., smoking, cleaning supplies, pets, air-conditioning, carpets, and other sources of irritants).

B. Ocular symptoms

Ocular symptoms are often nonspecific, such as tearing, irritation, stinging, burning, and photophobia as they involve the four classical signs of inflammation, calor (heat), dolor (pain), rubor (erythema), and tumor (swelling), in addition to tearing, irritation, stinging, burning, and photophobia. Symptoms tend to improve with cool, rainy weather and are exacerbated by warm, dry weather.

1. **Itching (pruritus)** is the hallmark of allergic conjunctivitis that can be mild or prominent and may last from hours to days; it is often described as mild to severe. Burning and grittiness may signify other forms of pathology such as dry eye. A stringy or ropy discharge is characteristic of a persistent ocular allergy and may range from serous to purulent. A purulent discharge, morning crusting, and difficulty opening the lids are characteristics of bacterial infection, especially with gram-negative organisms (e.g., *Neisseria* and *Haemophilus*). Environmental allergens typically affect both eyes at once, although a unilateral reaction may result if one eye is inoculated with animal hair or dander.
2. Most environmental allergen exposures are associated with bilateral symptoms, whereas a **unilateral conjunctival involvement** suggests an infectious etiology that is commonly associated with a palpable, ipsilat-eral preauricular node.
3. **Ocular pain** is not a feature of acute seasonal or perennial allergic conjunctivitis but suggests either an extraocular process such as a cor-neal abrasion, scleritis, or foreign body or an intraocular process such as uveitis, commonly associated with photophobia. The pain is *sharp* and sometimes piercing in character. Retro-orbital *dull* pain is associated with ethmoidal sinusitis.

C. Ocular examination

The examination starts with inspection of the face and area surrounding the eye to a more focused exam of the conjunctiva. A horizontal nasal skin crease ("allergic salute") suggests a diagnosis of allergic rhinitis. Scratches and scars on the face or eyelid suggest ocular injury. In addition, palpation of the sinuses and the preauricular, submandibular, and cervical chain lymph nodes are diagnostically important.

1. Eyelid, Periocular Tissue and Eyeball

a. Careful examination of periorbital tissue can demonstrate blepharitis, dermatitis, swelling, discoloration, ptosis, or blepharospasm. Eyelid or nasal vesicular eruptions are often seen in ophthalmic zoster but can also reflect recurrent bacterial infections, such as staphylococcal blepharoconjunctivitis secondary to constant rubbing of the eyelids. The subcutaneous layer contains loose areolar tissue and little subcutaneous fat, which allows the greatest potential for fluid accumulation leading to periorbital edema especially prominent around the lower lids due to the effects of gravity.

b. The normal eyelid just touches the iris (not the pupil). In exophthalmos, the eyelid does not touch the iris (note visible white of the sclera) with extension of the globe beyond the bony portion of the orbit. The ptotic eyelid covers most of the upper iris, approaching the pupil.

c. The junction point between the external and internal portion of the eyelid is the transition where the meibomian glands add the lipid component to the tear fluid. A rounded, plugged meibomian gland is consistent with a **hordeolum** (stye). Conjunctival involvement may present with chemosis, hyperemia, cicatrization, or papillae formation on the palpebral and bulbar membranes. The presence of increased or abnormal secretions should also be noted. Eversion of the upper eyelid requires experience to accomplish correctly (see III.B and Figure 7-3).

d. "Allergic shiners" are ecchymotic-looking areas beneath the eyes and may be confused with the "raccoon sign" associated with head trauma.

e. Skin of lids and/or face may demonstrate evidence of acne rosacea, seborrhea, psoriasis, or other dermatoses.

f. Palpation of the eyeball can demonstrate a hard "golf ball" texture and is consistent with increased intraocular pressure, which with associated pain or blurring of vision requires an immediate referral to an ophthalmologist.

2. Conjunctiva

a. The conjunctiva is composed of two immunologically active layers: the epithelial and substantia propria separated by the epithelial basement membrane. Mast cells (~6,000/mm^3), lymphocytes, and other inflammatory cells normally are found in the substantia propria, just below the junction with the epithelium. Normal ocular epithelia do not contain any mast cells, eosinophils, and basophils but are found in chronic ocular allergic inflammatory disorders.

b. A velvety, beefy-red conjunctiva suggests a bacterial cause, while a milky appearance—the result of obscuration of blood vessels by conjunctival edema—is characteristic of allergy. The bulbar and tarsal conjunctivae are examined for the presence of hyperemia, follicles, cysts, chemosis, hemorrhage, abrasion, ulcers,

foreign body, lacerations, and growths. The location of conjunctival redness is associated with specific disorders (Fig. 7-2).

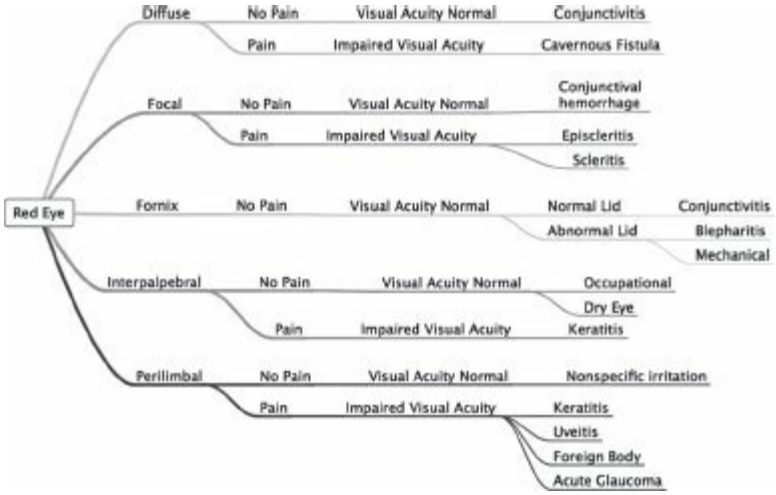

Figure 7-2. Flow chart of differential diagnoses of the red eye with the identification of the primary location of the redness as noted to be either diffuse, focal, in the fornix (portion where the palpebral conjunctiva meets the bulbar conjunctiva), interpalpebral (located between the upper and lower eyelids), and perilimbal (around the corneal–scleral junction).

3. Tear film

a. The conjunctival surface is bathed with a thin layer of tear film, which is composed of an outer lipid layer, a middle aqueous layer, and an inner mucoprotein layer. This mixture decreases the evaporation rate of the aqueous portion. A defect in any of the three portions leads to a form of dry eye syndrome.

b. Ocular secretions that are "sticky" (causing "glued" eyelids) or the presence of morning crusting are associated with infection. A clear, white, stringy or ropy discharge is seen with allergic etiologies. Any secretion in the conjunctival fornix is abnormal. Mucous adhering to the corneal or conjunctival surfaces is considered pathologic.

c. The cornea is best examined with a slit lamp biomicroscope, although many important clinical features can be seen with the naked eye or with the use of an ophthalmoscope. The cornea should be perfectly smooth and transparent. The application of fluorescein reveals corneal lesions with small spots indicating a form of keratitis, and a corneal defect suggests an erosion or an ulcer. The anterior chamber should be clear; clouding of the aqueous humor may be due to blood (hyphema) or the settling out of pus (hypopyon). An estimate of the anterior chamber depth can be made by illuminating it from the side with a penlight; if the iris creates a shadow, then there is a high index of suspicion for increased intraocular pressure (i.e., glaucoma) and an immediate referral to an ophthalmologist.

d. The **limbus** is the zone at the border of the cornea and the sclera and is the area that becomes intensely inflamed with a deep pink coloration in cases of anterior uveitis or iritis, the so-called ciliary flush. Discrete swellings with small white dots indicate degenerating cellular debris (**Trantas' dots or Horners' points**), commonly seen in vernal and atopic conjunctivitis.

e. Cataracts can be detected by funduscopic examination and are associated with atopic disorders and chronic corticosteroid use and/or intraocular inflammation. If detected, the patient should be referred to an ophthalmologist. The presence of a "red reflex" on funduscopic exam suggests normal light penetration to the posterior portion of the globe.

In contrast, a dullness or grey appearance suggests the presence of cataracts. Homogenous posterior cataracts are common with chronic steroid use, while anterior cataracts are reported with AKC.

f. The uvea is the most immunologically active tissue within the eye. The uvea comprises a continuous layer of iris, ciliary body, and choroid and possesses a rich vascular architecture and pigment within the alymphatic globe of the eye. The ciliary body is the production site of a filtrate, the aqueous humor, and is similar to other structures that produce a filtrate, including the renal glomerulus (urine) and the choroid plexus (cerebrospinal fluid). In addition, disturbances in aqueous humor production or outflow obstructions can cause increased intraocular pressure (i.e., glaucoma). These filtration sites are involved in clinical disorders associated with circulating immune complexes. Although there is a paucity of mast cells within the uveal tissue, there is a notable increase in mast cell numbers in uveitis. However, the predominant inflammatory cell type in uveitis is the lymphocyte.

g. Immunologic involvement of the optic nerve is commonly associated with pain on movement in patients with optic neuritis while the ischemic events of **temporal arteritis** can be associated with painless loss of vision ("amaurosis fugax").

III. PROCEDURES

A. Ophthalmoscopy

The direct (handheld) ophthalmoscope provides approximately 14× magnification. The ophthalmoscope lens settings of +8 will assist the physician in focusing on the anterior segment to reveal corneal opacities or changes in the iris or lens. Decreasing the power of the lens from +8 to -8 will increase the depth of focus so that the examiner can move from the anterior segment progressively through the structures including the vitreous and reach the retina. The green light filter delineates small aneurysms and hemorrhages as black seen in autoimmune disorders (e.g., Systemic Lupus Erythematosus, vasculitis).

B. Eversion of the upper eyelid

Examination of the palpebral conjunctiva is performed in a stepwise fashion (Fig. 7-3). Eversion of the lower lid is simply performed by having the patient look upward while the lower eyelid is drawn downward with examiner's index finger applied to the orbital portion. This procedure is helpful when looking for papillary and follicular development in patients with more chronic forms of conjunctivitis.

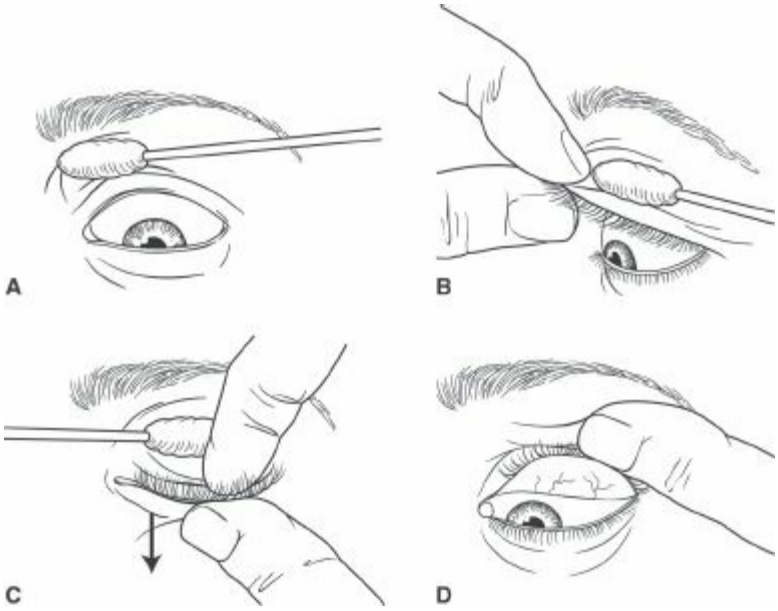

Figure 7-3. Eversion of eyelid: Eversion of the upper lid is performed by the placement of a cotton-tipped swab above the eyelid **(A)** and then, while the patient is asked to look downward, the upper eyelash is gently grasped **(B)**. The upper eyelid is gently pulled down while placing pressure on the upper portion of the eyelid with the cotton swab **(C)**, and then it is lifted over the surface of the swab **(D)**.

C. Dry eye tests

1. The Schirmer tear test with preprinted measures (Eagle Vision, 8500 Wolf Lake Drive, No. 110, Memphis, TN 38133, USA) is the most commonly used and easily performed test for the evaluation of dry eye (tear film dysfunction) (Fig. 7-4).

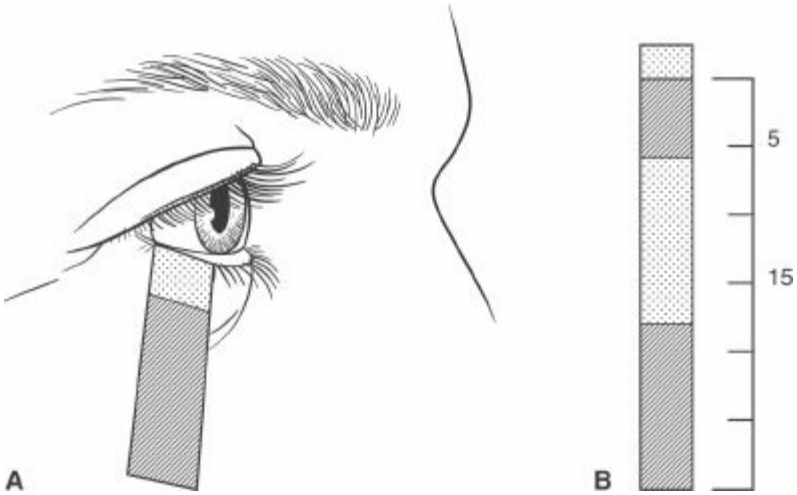

Figure 7-4. Schirmer's test: The rounded end of the test strip is bent at the notch approximately 90 to 120 degrees and is hooked into the conjunctival sac at the junction of the middle and lateral one-third of the lower eyelid margin. The test strips are removed after 5 minutes. Schirmer's I test (without anesthesia) measures both basal and reflex tearing. A measurement of ≤5 mm of wetting after a 5-minute time interval is considered abnormally dry. The normal range is 5 to 15 mm in 5 minutes. Tear production in excess of 25 mm may also represent the reflexively increased tear production seen in many patients with dry eye syndrome.

2. The development and availability of new technology (TearLab; FDA 510(k) k083184) enables the clinician to collect and measure osmolarity in 50 nL sample with minimal disturbance of the tear film using a handheld device (TearLabs, www.tearlab.com).

D. Staining procedures

1. **Fluorescein staining** is the best clinical means of diagnosing the presence of corneal epithelial surface defects and can be used to examine the cornea, conjunctiva, precorneal tear film, and tear breakup time. Fluorescein is applied (Fluor-I-Strip, Ayerst Laboratories, Inc., Philadelphia, PA) via strip or with a liquid dropper and examined

using a cobalt blue filter to best appreciate the staining pattern of the conjunctiva and cornea. Of note, soft contact lenses must be removed prior to fluorescein instillation to prevent their permanent staining. It is important to wait at least 1 hour after completion of the examination before replacing the soft contact lenses.

2. **Rose bengal** (RoseGlo—Wilson Ophthalmic Corp, Mustang, OK), a derivative of fluorescein, stains only dead and degenerating (not denuded) epithelium of the conjunctiva and cornea. Rose bengal causes stinging and can stain facial skin and clothing quite easily. Both rose bengal and **lissamine green** stain dead or degenerating epithelial cells and mucous. Lissamine green has the advantage over rose bengal to fade relatively quickly and to be nonirritating.

E. Conjunctival cytodiagnosis

1. Tear cytology is rapid and easy to perform: A few microliters of tears collected from the external canthus with a glass capillary are immediately placed on a precolored slide. The presence of even one eosinophil is highly indicative of an allergic pathology, while their absence does not exclude an allergic diagnosis. Tear immunoglobulin E (IgE) tests are not yet available for office measurement.

2. Conjunctival scraping is performed by scraping the conjunctiva with a spatula and looking for the differentiation of intracytoplasmic inclusion bodies. This procedure is performed when there is a suspicion of *Chlamydia* or in combination with immunofluorescence when looking for viruses.

3. Conjunctival biopsy is required for histologic and immunohistochemical analyses necessary for diagnosis of autoimmune diseases such as ocular pemphigoid.

IV. SPECTRUM OF MAST-CELL MEDIATED DISORDERS OF THE EYE

Ocular allergy includes several overlapping conditions that include seasonal (intermittent < 4 weeks of symptoms) and perennial (persistent > 4 weeks in duration) allergic conjunctivitis, vernal conjunctivitis, giant papillary conjunctivitis, and AKC, all of which appear to be part of a clinical spectrum ranging from acute non–sight-threatening to chronic sight-threatening disorders. This clinical spectrum can best be viewed from the perspective of immunologic changes that occur in the conjunctival surface. In **seasonal allergic conjunctivitis**, the change is a visible increase in the type and number of cells provoking allergy symptoms at particular times of the year. These cells include mast cells, eosinophils, and other cells that interact and release a variety of allergic mediators including histamine, leukotrienes, and prostaglandins when exposed to various airborne allergens (aeroallergens). In contrast, **perennial allergic conjunctivitis** is associated with a persistent increase in the number of these allergy-mediating cells throughout the year. In **vernal conjunctivitis**, there is a seasonally recurrent increase in mast cells, eosinophils, and lymphocytes. **Giant papillary conjunctivitis** has similar features but is directly related to the presence of objects irritating the eye, such as contact lenses. Finally, in **AKC**, there is chronic invasion of the immune cells into the conjunctiva that is seen in middle-aged and older patients with extensive allergic disorders, specifically eczema and asthma. Although contact conjunctivitis is purely a lymphocytic-mediated type of reaction like other delayed type hypersensitivity reactions, it is also presented in this section as a common clinical hypersensitivity reaction seen

by the allergist/clinical immunologist. Table 7-2 provides an overview of the spectrum of ocular allergic disorders, their signs and symptoms, and their salient features. Table 7-3 describes various inflammatory conditions that involve either the outside or the inside of the eye. The table focuses on the signs and symptoms of external causes of the red eye, which include the predominant cell type found in the conjunctival scraping, the presence or absence of chemosis, lymph node involvement, cobblestoning of the conjunctival surface, discharge, lid involvement, pruritus, gritty sensation, and seasonal variation.

Table 7-2 Spectrum of Ocular Allergy Disorders

Type	Signs/Symptoms	Salient Features
Seasonal, intermittent allergic conjunctivitis	Moderate-to-severe pruritus Mild-to-moderate diffuse conjunctival injection Lid swelling and conjunctival chemosis Involvement <4 wk in duration <4 d a wk	Family and personal history of atopy Most common type of ocular allergy More than 50% of allergic rhinitis patients also have ocular symptoms Pollen sensitivity is the most common cause
Perennial, persistent allergic conjunctivitis	Conjunctival injection and edema Year-round symptoms Majority of patients have seasonal exacerbations Eosinophils in scrapings Involvement >4 wk in duration >4 d a wk	Family and personal history of atopy Predominantly seen in adults Often associated with a specific environment (pollen, animal dander, dust mites at home, industrial allergens at work)
Vernal conjunctivitis	Severe pruritus Ropy, stringy discharge Palpebral variety: cobblestone papillae covering upper tarsus Limbal variety: limbal infiltrates and nodules Trantas' dots (Horners' points) Untreated corneal complications (shield ulcer) may result in scarring and permanent visual impairment Appears from early spring until fall	80% of patients <14 years old Usually "outgrown" by late teens or early 20s 75% patients are male More common in dry, warm climates (e.g., Mediterranean basin, northern Africa)
Giant papillary conjunctivitis	Decreased tolerance to contact lenses Blurred vision Conjunctival hyperemia Late stage: giant papillae or follicles (up to 0.3 mm), pain, foreign body sensation, increased mucus production	Trauma induced by contact lenses, ocular prosthetics, exposed sutures
Atopic keratoconjunctivitis	Severe itching, burning, photophobia Erythematous, eczematous eyelids Superficial punctate keratitis Superficial corneal infiltrates Perennial symptoms May be exacerbated in winter	Food, dust mite, pollen, animal dander sensitivity Associated with atopic dermatitis activity Begins in late teens or early 20s

Table 7-3 Differential Diagnosis of Conjunctival Inflammatory Disorders

	AC	VC	AKC	GPC	Con-tact	Bacterial	Viral	Chla-mydial	KCS	BC
Signs										
Predominant cell type	Mast cell, Eos	Lymph, Eos	Lymph, Eos	Lymph, Eos	Lymph	PMN	PMN, mono, lymph	Mono, lymph	Lymph, mono	Mono, lymph
Chemosis	+	+/ –	+/–	+/–	–	+/–	+/–	+/–	–	+/–
Lymph node	–	–	–	–	–	+	++	+/–	–	–
Cobblestoning	–	++	++	++	–	–	+/–	+	–	–
Discharge	Clear, mucoid	Stringy, mucoid	Stringy, mucoid	Clear, white	+/–	++ Mucopu-rulent	Clear, mucoid	++ Mucopu-rulent	+/– Mucoid	++ Mucopurulent
Lid involvement	–	+	+	–	++	–	–	–	–	++
Symptoms										
Pruritus	+	++	++	++	+	–	–	–	–	+
Gritty sensation	+/–	+/–	+/–	+	–	+	+	+	+++	++
Seasonal variation	+	+	+/–	+/–	–	+/–	+/–	+/–	–	–

AC, Allergic conjunctivitis; VC, vernal conjunctivitis; AKC, atopic keratoconjunctivitis; GPC, giant papillary conjunctivitis; KCS, keratoconjunctivitis sicca; BC, blepharoconjunctivitis; PMN, polymorphonuclear cell; Mono, monocyte; Lymph, lymphocyte; Eos, eosinophil.

A. Seasonal/intermittent and perennial/persistent

1. **Basic mechanisms.** Because of the direct exposure of the ocular mucosal surfaces to the environment, mast cell– and IgE-mediated reactions are the most common hypersensitivity responses of the eye. Approximately 50 million mast cells are in the ocular and adnexal tissue in each human eye. Conjunctival angioedema is frequently seen in hypersensitivity reactions, and conjunctival late-phase reactions can occur.
2. **History, physical examination, laboratory findings, and differential diagnosis.** Seasonal and perennial allergic conjunctivitis are the most prevalent forms of ocular allergy, with seasonal allergic conjunctivitis being more common. Grass pollen produce more ocular symptoms than other aeroallergens. Conjunctival symptoms include itching, tearing, and burning as well as corneal symptoms of photophobia and blurring of vision. Clinical signs of allergic conjunctivitis include milky or pale pink conjunctivae with vascular congestion, which can progress to conjunctival swelling (**chemosis**). A white exudate can form during the acute state, which becomes stringy in the chronic form. Tears can contain histamine and a small number of eosinophils.

B. Atopic keratoconjunctivitis

1. **Basic mechanisms.** AKC is mediated by a mixture of mast cell, IgE, and lymphocytic interactions along with infiltrations of basophils, eosinophils, plasma cells, and lymphocytes.
2. **History, physical examination, laboratory findings, and differential diagnosis.** A family history of atopy and its association with atopic dermatitis is common. Symptoms include itching, burning, and tearing. Signs found on physical exam include pale conjunctivae and limbal infiltration (Horners' points or Trantas' dots). Laboratory evaluation of the tears can demonstrate the presence of IgE, eosinophils, and mononuclear cells with a paucity of basophils and mast cells. Other abnormalities include increased basophil histamine release, peripheral eosinophilia, and an elevated serum IgE.
3. **Complications (sight threatening).** Corneal ulceration and scarring, retinal detachment,

keratoconus, and cataract formation (8%) can occur in AKC patients. Cataracts are associated with this disease and predominantly involve the anterior portion of the lens and can evolve rapidly into complete opacification within 6 months. Many patients may develop secondary staphylococcal blepharitis.

4. **Treatment** usually requires a multidisciplinary approach in consultation with an ophthalmologist. Cool compresses are often of limited symptomatic benefit to the patient. Acute exacerbations may require topical and systemic steroids. Topical and sometimes systemic cyclosporine may be required for long-term control. Immunotherapy and mast cell stabilizers with antihistamine activity have been reported in studies to be an adjunctive treatment modality in patients clearly having a seasonal component. Immunotherapy has no apparent effect on the progression of the disease.

C. Vernal conjunctivitis

1. **Basic mechanisms.** Histopathologically, vernal conjunctivitis is characterized by conjunctival infiltration with eosinophils, degranulated mast cells, basophils, plasma cells, lymphocytes, and macrophages, supporting the hypothesis that vernal conjunctivitis is a combined mast cell–, IgE-, and lymphocyte-mediated hypersensitivity reaction. As the disease progresses, fibrous tissue proliferates to generate the giant papillae. Mucosal mast cells are increased in the conjunctiva of these patients. Degranulated eosinophils and their proinflammatory enzymes (e.g., major basic protein) are found in the conjunctiva and in the periphery of corneal ulcers, suggesting an etiologic role in many of the associated problems.
2. **History, physical examination, laboratory findings, and differential diagnosis.** Vernal conjunctivitis commonly begins in the spring (also referred to as vernal catarrh). Symptoms include **intense pruritus** exacerbated by length of exposure, type of exposure (wind, hot weather, dust, or bright light), or physical exertion associated with sweating. Associated symptoms involving the cornea include photophobia, foreign body sensation, and lacrimation. Signs on physical exam include conjunctival hyperemia with papillary hypertrophy ("cobblestoning") reaching 7 to 8 mm in diameter of the upper tarsal plate; a thin copious milk-white fibrinous secretion composed of eosinophils, epithelial cells, and Charcot–Leyden granules; limbal or conjunctival yellowish-white points known as Horners' points and Trantas' dots lasting 2 to 7 days; an extra lower eyelid crease or a Dennie's line; corneal ulcers infiltrated with Charcot-Leyden crystals; or pseudomembrane formation of the upper lid when everted and exposed to heat (Maxwell-Lyon sign). Although vernal conjunctivitis is a bilateral disease, it can affect one eye more than the other. The most common corneal degenerative change seen is pseudo-gerontoxon (arcus senilis), whereas the most severe is corneal ulceration.
3. **Natural history.** Vernal conjunctivitis is a disease of childhood appearing more commonly in prepubertal boys. Onset after puberty is equally distributed among the sexes and dissipates by the third decade of life (about 4 to 10 years after onset).
4. **Treatment** requires a multidisciplinary approach in consultation with an ophthalmologist. Cool compresses to the eyes can benefit the patient. Oral and topical steroids have been the primary treatment. Topical and sometimes systemic cyclosporine permit a steroid-

sparing effect in VC treatment. Immunotherapy and mast cell stabilizers with antihistamine activity can be used as adjunctive treatment in patients clearly having a seasonal component.

D. Giant papillary conjunctivitis

1. **Basic mechanisms.** Infiltrations of basophils, eosinophils, plasma cells, and lymphocytes suggest a mixed mast cell– and lymphocyte-mediated process associated with the continued use of contact lenses. The etiology remains controversial.
2. **History, physical examination, laboratory findings, and differential diagnosis.** Typically, symptoms increase during the spring pollen season; the major symptom is itching. Signs on physical exam include a white or clear exudate upon awakening that becomes thick and stringy, and the patient may develop Horners' points and Trantas' dots, limbal infiltration, and bulbar conjunctival hyperemia and edema. Upper tarsal papillary hypertrophy (cobblestoning) is seen in 5% to 10% of soft contact and 3% to 4% of hard contact lens wearers. Although this condition is most commonly seen in patients wearing contact lenses, it is also seen in patients with other foreign materials around the orbit (e.g., ocular sutures, scleral buckles, or prosthetics).
3. **Treatment** primarily is avoidance of the inciting process (i.e., removal of the contact lens), but when this is impractical, cromolyn sodium and topical corticosteroids can be useful.

V. DIFFERENTIAL DIAGNOSIS OF CONJUNCTIVITIS

Conditions that commonly are associated with pink eye include a spectrum of disorders affecting the eyelid, including contact lens use, dry eye syndromes, trauma, and chemical irritation (Table 7-4). Other than allergic and immunologic disorders causing a "pink" or "red" eye, infectious conjunctivitis is frequently encountered and can have a similar clinical picture to various forms of ocular allergy. Drainage is the key for infectious causes with "glue eye" and crusting in the morning.

Table 7-4 Differential Diagnoses of Pink Eye

Other types of conjunctivitis

Type	Causes	Signs	Symptoms	Comments
Blepharitis (Blepharo-conjunctivitis)	- Chronic staphylococcal infection of the eyelids	-Scaling of eyelashes - Missing eyelashes - Swollen eyelids	-Itchy, crusted eyelids - Redness, irritation worse on awakening	- Common cause of chronic conjunctivitis
Contact lens	- Allergy - Tissue hypoxia - Giant papillary conjunctivitis	- Secondary changes in conjunctiva and cornea - Hyperemia	- Mild itching	- Can be acute or chronic, allergic or nonallergic
Dry eye syndromes (keratocon-junctivitis sicca)	- Decreased tear production, distribution, or absorption - Poor tear quality - Medications (anticholinergics, antihistamines, oral contraceptives) - Sjögren's syndrome	- Abnormal conjunctival thickening - Vision usually preserved - Pupils reactive to light - Hyperemia - No corneal involvement	- Mucous discharge - Bilateral itching - Foreign body sensation - Mild pain - Intermittent watering	- More common in women and older persons
Mechanical	- Entropion - Eyelashes - Trichiasis - Foreign bodies - Sutures	- Conjunctival hyperemia (focal or diffuse)	- Tearing - Foreign body sensation	- Chronic irritation leads to secondary conjunctivitis
Traumatic	- Direct (corneal abrasions, lacerations, epithelial defects) - Indirect (chemical) injury	- Conjunctival hyperemia	- Tearing - Foreign body sensation	- May resemble noninfectious secondary conjunctivitis - Corneal abrasion may signify presence of herpes simplex
SubconJuctival hemorrhage	- Trauma - Hypertension - Straining - Severe coughing - Atherosclerosis - Bleeding disorders - Medication (warfarin)	- Normal vision - Pupils equal and react to light - Bright red patch on sclera - No corneal involvement	- Pain absent or mild - No discharge	- Harmless and self-limited
Chemical burn	- Oven cleaner - Drain cleaner - Cement - Plaster powder, etc.	- Diminished vision - Corneal involvement is common	- Severe pain - Red eye - Photophobia	- Corneal involvement is common

A. Dry eye syndromes

1. **Dry eye syndrome** (tear film dysfunction) is one of the most common disorders of the eye and is frequently confused with allergic conjunctivitis in the adults. True dry eye develops from decreased tear production, increased tear evaporation, or an abnormality in specific components of the aqueous, lipid, or mucin layers that comprise the tear film. Decreased tear production commonly occurs secondary to long-term use of contact lenses, certain medications (first-generation antihistamines and psychotropic agents, e.g., phenothiazines, anti-cholinergics, chemotherapeutic agents), computer use (decreased blinking), chronic blepharitis, fifth or seventh cranial nerve palsies, vitamin A deficiency, and pemphigoid. This disorder frequently occurs concomitantly with ocular allergic disorders and is exacerbated by use of oral antihistamines. Symptoms of dry eye are typically vague and include foreign body sensation, easily fatigued eyes, dryness, burning, ocular pain, photophobia, and blurry vision. Symptoms tend to be worse late in the day after prolonged use of the eyes or exposure to environmental conditions. Treatment includes the chronic use of lubricants (preferably preservative-free) and topical cyclosporine and may also require a short course of topical steroids.
2. **KCS** is commonly associated with underlying systemic immune disorders such as Sjögren's syndrome, rheumatoid arthritis, and human immunodeficiency virus (HIV)

infection. In addition, it is notably diagnosed in postmenopausal women. KCS is characterized by insidious and progressive dysfunction of the lacrimal glands. Patients initially complain of a mildly injected eye with excessive mucus production. Symptoms include a gritty, sandy feeling in the eyes as compared to the itching and burning feeling many patients complain with ocular allergy. Symptoms worsen throughout the day as the limited portion of the aqueous tear film evaporates. Exacerbation of symptoms occurs in the winter months when heating systems decrease the relative humidity in the household to <25%.

3. **Hormonal-associated conjunctivitis** occurs with hormone-associated alteration in tear fluid composition leading to conjunctivitis. It is commonly associated with age and changes of the hormonal homeostasis among pregnant, peri- and postmenopausal women demonstrating changes in conjunctival epithelium morphology similar to other dry eye syndromes (menopausal KCS).

B. Eyelid dermatitis

1. The clinical presentation of eyelid dermatitis (itching, scaling, swelling, weeping exudate) is a common problem. Atopic dermatitis of the eyelids is the most common cause of chronic eyelid dermatitis; up to 39% of patients with eyelid dermatitis have a history of atopy. Contact dermatitis occurs more commonly than irritant contact dermatitis in older female patients. The frequency of ocular rosacea ranges from 3% to 58% of patients with rosacea, with peak age of onset being later than cutaneous rosacea (51 to 60 years). Seborrheic dermatitis (SD) of the eyelids is common with greasy, patchy, erythematous scaly eyelid margins. Eyelid psoriasis is uncommon, and the symptoms are nonspecific and may be a marker of more severe psoriasis.

C. Dermatoconjunctivitis

1. **Basic mechanisms.** Dermatoconjunctivitis is a delayed-type hypersensitivity reaction invoking an intense lymphocyte-mediated conjunctival reaction, frequently occurs in response to long-term use of topical ocular therapies (eye drops, ointments, contact lens solutions, etc.) and is often caused by the preservatives in these ophthalmic solutions.
2. **History, physical examination, laboratory findings, and differential diagnosis.** Delayed hypersensitivity reactions that involve the eyelids causes the patient to seek medical attention more often than for cutaneous reactions elsewhere on the skin. The eyelid skin is soft, pliable, and thin, which increases the eyelid's susceptibility to contact dermatitis. The eyelid skin develops significant swelling and redness with minor degrees of inflammation. Preservatives such as thimerosal in contact lens cleaning solutions are the major culprits. This condition typically improves when the patient changes to preservative-free cleaning solutions.

D. Drug-induced conjunctivitis

1. **Drug-induced conjunctivitis** can be caused by several medications, including neomycin, antiglaucoma agents, pamidronate, erectile dysfunction agents, cytosine, and herbal medications. The reactions induced by topical medications often occur in the lower eyelid and inferior conjunctiva, as these medications tend to pool in these areas. Patients usually present with red-colored inflamed conjunctiva, papillae development, pinpoint keratitis, and chemosis. Contact dermatitis is the most common eruption of the eyelid, which is most

often caused by cosmetics applied to the hair, face, or fingernails rather than by cosmetics directly applied to the eye area. These cosmetics typically do not cause a reaction when applied to other sites; this is particularly true for hair dye and nail polish. Allergic and irritant reactions to face creams, makeup, and blushes may likewise be limited to the eyelids. Transitory stinging and burning of the eyes and lids on application of an eye-area cosmetic are the most common complaints. Common causes of these symptoms include evaporation of volatile components (such as mineral spirits, isoparaffins, and alcohol) and potential irritants (such as propylene glycol and soap emulsifiers) in eye-area formulations.

2. **Diagnosis.** The patch-test response to allergens and irritants may likewise be indistinguishable. Either allergens or irritants can elicit erythema and/or edema at the patch-test site. Less common is an eczematous vesicular reaction diagnostic of delayed allergic hypersensitivity response. Interpretation of patch-test results may consequently be difficult, and the likelihood of irritant false-positive reactions must be borne in mind.

E. Conjunctivitis medicamentosa

A specific form of drug induced conjunctivitis that parallels the occurrence in the nose is conjunctivitis medicamentosa. In this condition, there is increased conjunctival injection and rebound hyperemia that follows the overuse (weeks to months in duration) of vasoconstricting eye drops. Treatment includes the use of short courses of topical steroids while withholding the potential inciting agent.

F. Seborrheic dermatitis

SD is a common chronic and recurrent macular condition of skin characterized by symmetric erythematous greasy (sometimes crusting) scaling that can involve the periocular tissue (e.g., seborrheic blepharitis involving the eyebrows and eyelids) with the scalp, ears, sides of the nose, chest, axilla, and inguinal area also being involved. Malassezia (previously Pityrosporum) yeast are associated with an altered immune response or as the result of hyperproliferation. Ocular complications of chronic seborrhea of the eyelids include hordeola (styes) and inflammation of the meibomian glands (meibomitis) with secondary conjunctivitis (blepharoconjunctivitis). Uncontrolled severe SD is seen in HIV patients and can be the initial presentation of the disease. Mild-strength topical steroid creams can be used sparingly, but due to the increased risk of steroid-associated side effects, only short courses or steroid-sparing remedies should be used. Calcineurin inhibitors (e.g., pimecrolimus [Elidel™], tacrolimus [Protopic]) are effective, but their safety in children younger than 2 years is controversial (with noted increased conjunctival irritation). Improved periocular hygiene with saline compresses and baby shampoo wiped gently on the affected areas help alleviate the scaling and crusting of blepharitis. Topical antifungal creams, shampoos, and lotions containing selenium sulfide and zinc pyrithione can be helpful.

G. Rosacea

Rosacea is often mistaken for acne, but the major difference is the lack of comedones. Rosacea consists of erythema, edema, papules, pustules, or telangiectasias occurring on the cheeks, forehead, nose, and eyes. Rhinophyma is characterized by a bulbous appearance with chronic inflammation and hypertrophy of the nose. Precipitating factors include consumption of alcohol or hot beverages, spices, sun exposure, and stress that lead to “a chronic blush.” Nonspecific

symptoms may include conjunctivitis, blepharitis, soreness, lacrimation, and grittiness. Aside from involvement of the lid (blepharitis, chala-zion), ocular rosacea can involve the conjunctiva (conjunctivitis, KCS), sclera (scleritis, episcleritis, scleral perforation), iris (iritis, iridocyclitis), and cornea (punctuate keratopathy, scarring, corneal perforation, corneal neovascularization, ulceration, and blindness). Approximately 18% of acne rosacea patients have signs or symptoms of ocular rosacea, and 20% have ocular manifestations before the skin lesions; this occurs more often in women.

H. Seborrheic keratosis

Seborrheic keratosis are very common benign cutaneous growths that are skin colored to hyperpigmented and commonly involve the eyelids. They are seen with increasing age and are well-circumscribed, thick, keratotic papules or plaques that can have a smooth, flat surface or an irregular rough surface. They are benign and not related to sun exposure. A genetic form is common in blacks and is termed dermatosis papulosa nigra.

I. Occupational conjunctivitis

1. Occupational conjunctivitis refers to ocular symptoms arising in response to airborne substances in the workplace, mediated by allergic (e.g., laboratory animal antigen, grain) and/or nonallergic factors (e.g., jet cabin air, organic chemicals, and irritants). Case reports have also been attributed occupational conjunctivitis to wool, plants, coconut fiber dust, fish parasite, detergent protease, and white pepper. It often coexists with occupational rhinitis and asthma.

VI. IMMUNOLOGICAL DISORDERS ASSOCIATED WITH OCULAR FINDINGS

Ocular inflammation can result in increasing visual loss as it proceeds from the anterior portion to the posterior portion of the eye.

A. Uveitis

Although ocular allergy is the most common form of ocular inflammation, anterior uveitis is the most common form of intraocular inflammation. Intraocular inflammation is described by location, with anterior uveitis involving all structures anterior to and including the lens–iris diaphragm. Posterior segment intraocular inflammation (posterior uveitis) involves the structures behind the lens–iris diaphragm such as the ciliary body, retina, and choroid. Some disorders involve both portions and are called panuveitis. Anterior uveitis is commonly classified as (1) autoimmune (idiopathic) affecting the eye only, (2) associated with a systemic disease, or (3) associated with trauma. Anterior uveitis is frequently unilateral and can be self-limiting, but when it is associated with a systemic immune disorder, it is often more chronic, recurrent, and can be bilateral. Uveitis is not to be confused with another form of intraocular inflammation called **endophthalmitis**, which is an infectious form of uveitis, that is, where the infection is the major cause of inflammatory response leading to tissue damage. However, some forms of infections may cause intraocular inflammation predominantly through a cross-reaction to antigens rather than a direct infection; examples of this include uveitis associated with tuberculosis or syphilis. However, a staphylococcal infection causes major destruction through direct tissue invasion. The choroid contains a sparse collection of B and T lymphocytes, mast cells, and fibroblasts. When inflamed, it becomes densely populated with

plasma cells, phagocytes, and B and T lymphocytes, which can form pseudolymphoid follicles or granulomas with some cells entering the aqueous humor. A variety of specific uveal antigens are capable of inducing uveitis. Examples include the soluble S antigen (molecular weight 55 kDa) and opsin retinal proteins.

1. Clinical features, symptoms, and signs

a. Common clinical features of anterior uveitis include inflammatory cells and protein exudate floating in the anterior chamber. When the inflammation is severe, there can be deposition of cells and protein on the endothelial surface of the cornea (keratic precipitates). The inflammatory process can be classified by predominant cell type, for example, nongranulomatous (predominantly neutrophil) or granulomatous (predominantly lymphocyte and macrophage). The ciliary body is commonly involved and is accompanied by miosis, dilatation, and engorgement of the ciliary vessels (ciliary injection).

b. The symptoms of anterior uveitis depend on the underlying inflammatory processes that occur and their location. Blurred vision is caused by cellular infiltrates and protein exudates into the anterior chamber. Photophobia and glare are caused by corneal epithelial edema, infiltration of cells and protein into the anterior chamber, and ciliary muscular spasm. Pain is an important sign indicating intraocular inflammation but is not associated with the conjunctival inflammation from ocular allergies. Pain can vary from mild to severe; severe pain occurs with ciliary muscle spasm. With persistent ocular pain, the patient can develop a dull aching sensation in the eye or a generalized headache. Periorbital pain and/or tenderness on palpation of the eye should raise the concern for increased intraocular pressure (i.e., glaucoma), whereas pain with either palpation or movement of the eye is a sign of inflammation of the outer sheath of the eye (i.e., scleritis). Tearing is a common symptom and is related to the stimulation of the parasympathetic nerves.

c. The signs of anterior uveitis include lid edema or even pseudoptosis; injection with a ciliary distribution (i.e., increasing intensity of the injection from the periphery to the corneal–scleral junction) appears to have a purplish hue. Notably, the conjunctival surface remains relatively clear, whereas conjunctival injection appears to be more intense and distributed more peripherally than at the corneal–scleral junction. Conjunctival injection can involve both the conjunctival and palpebral surfaces. When the inflammation is intense, a large number of inflammatory cells accumulate in the form of a **hypopyon**. Miosis is usually a sign of ciliary muscle spasm but may also be due to adhesion of the inflamed iris to the anterior lens capsule (posterior synechia). With miosis, synechia can also form between the iris and the cornea within hours. Severe inflammation of the iris leads to engorgement of the fragile iris blood vessels and possibly a localized hemorrhage that forms a hyphema. Direct iris infiltration with accumulation of inflammatory cells can lead to nodular lesions within the iris (Busacca's nodules) or at the rim of the pupil (Koeppe's nodules). Increased intraocular pressure is common and caused by inflammatory cell infiltration, edema, and ciliary body detachment. Cataract formation is the most common complication of anterior uveitis.

d. Clinical immunologic investigation

(1) The immunologic investigation of the patient with anterior uveitis includes

inquiring about recent infection with gram-negative organisms or viruses (including HIV) and symptoms associated with systemic disease, such as joint symptoms, mucosal lesions (aphthous ulcerations), and respiratory symptoms. In addition, it is important to inquire about the patient's potential for being immu-nosuppressed. The following tests are recommended prior to starting any systemic immunomodulatory treatment: complete blood count with differential and platelets; 24-hour urine collection for protein, creatinine (creatinine clearance) for evidence of glomerulonephritis associated with various autoimmune disorders, and calcium for hypercalciuria associated with sarcoid; erythrocyte sedimentation rate and C-reactive protein (general markers of inflammation associated with rheumatoid arthritis and vasculitis); serum chemistries including blood urea nitrogen, liver enzymes, electrolytes, angiotensin converting enzyme levels (associated with chronic granulomatous disorders such as sarcoid or granulomatous infections); a urinalysis for glucose; a chest radiograph and a tuberculin skin test with a full anergy panel for the possible infection with tuberculosis or histoplasmosis (and to assess for anergy that can be seen in sar-coid and HIV infection and the possible pathergic response seen in Behçet's disease). One should also consider doing specific tests that focus on the presence of certain physical findings, such as;

(i) Cutaneous eruptions and arthritis: include various antibody assays for autoimmune disorders such as systemic lupus erythematosus, Wegener's granulomatosis, anticardiolipin syndrome, and infectious disorders such as Lyme's disease or syphilis (antinuclear antibodies, antineutrophilic cytoplasmic antibodies, lupus anticoagulant, anticardiolipin antibodies, serology for Lyme's disease and syphilis)

(ii) Genitourinary tract symptoms: include culture for nonspecific urethritis (chlamydial and gonococcal infections)

(iii) Gastrointestinal symptoms: include endoscopy and colonoscopy/biopsy to evaluate for possible inflammatory bowel disease (Crohn's disease)

Close cooperation with the ophthalmologist is necessary to maximize the clinical outcome.

B. Kawasaki's disease (KW)

Also known as mucocutaneous lymph node syndrome, Kawasaki's disease is an acute exanthematous illness that almost exclusively affects children, with 50% predominantly occurring in boys below the age of two and increased in the Japanese. One of the six major criteria is bilateral nonexudative conjunctival injection with other ocular findings including anterior mild, bilateral, and symmetric uveitis in 66% of patients and superficial punctate keratitis in 12% of patients. Vitreous opacifications, choroiditis, and papilledema can also occur.

C. Immunodeficiencies

1. **Ataxia-telangiectasia** presents with large tortuous vessels on the bulbar conjunctiva, most prominent in the exposed canthal regions. This finding typically becomes evident between 1 and 6 years of age and can become more prominent with time.
2. **HIV AIDS** is associated with primarily infectious complications with cyto-megalovirus (CMV) retinitis being one of the most frequently encountered disorders. It affects

approximately 7% of children with HIV AIDS and can lead to permanent vision loss if untreated. CMV retinitis is characterized by regions of intraretinal hemorrhage and white areas of edematous retina. HIV cotton-cotton-wool spots retinitis, herpes zoster retinitis, and toxo-plasmosis retinitis can occur in children. Dry eye syndromes are increased as there is common involvement of the lacrimal gland.

D. Autoimmune disorders

1. **Pemphigoid and pemphigus.** Pemphigoid of the eye, known as cicatricial pemphigoid, has a similar histopathologic picture to bullous pemphi-goid of the skin, in that the desmosomal attachments between epithelial cells are lysed. IgG and IgA bind to the basement membrane in 80% of patients. When the subepidermal blister ruptures, an overgrowth of fibrous tissue occurs, leading to severe corneal damage, dry eyes, neovas-cularization with fibrosis, and subsequent loss of vision. The denuded conjunctival epithelium leads to adhesions termed symblepharons, interfering with closing of the eyelids and the mucous-producing goblet cells. Similar to pemphigoid, pemphigus vulgaris is mediated by complement-fixing IgG to intercellular cement substance producing acantholysis and intraepithelial blisters all over the body, including the skin, mouth, and eyes. Lesions of the eye commonly involve the conjunctivae. The bursting of the bullae is painful though the area usually heals without sequelae.

VII. OVERVIEW OF OCULAR ALLERGY TREATMENT

Allergic conjunctivitis treatment: An overview of the treatment of ocular allergic disorders is provided in Table 7-5. General considerations of treatment of ocular allergic disorders include the following:

Table 7-5 Ocular Allergy Treatment Algorithm

Therapeutic Intervention	Clinical Rationale	Pharmaceutical Agents	Comments
Primary			
Avoidance	Effective Simple in theory Typically difficult in practice		>30% symptom improvement
Cold compresses	Decrease nerve C fiber stimulation Reduce superficial vasodilation		Effective for mild to moderate symptoms
Preservative-free tears	Lavage, dilutional effect	Artificial tears	Extremely soothing Recommend refrigeration to improve symptomatic relief Inexpensive OTC Safe for all ages Comfortable Use as needed
Secondary			
Topical antihistamine and decongestants	Antihistamine relieves pruritus Vasoconstrictor relieves injection	Antazoline–naphazoline Pheniramine–naphazoline	Quick onset More effective than systemic antihistamines Limited duration of action Frequent dosing required
Topical antihistamine and mast cell stabilizer	Single agent with dual action Has immediate and prophylactic activity Eliminates need for two-drug therapy Comfort enhances patient compliance	OTC Ketotifen (Zaditor™) Rx Olopatadine (Pataday™) Azelastine (Optivar™) Bepotastine (Bepreve™) Alcaftadine (Lastacaft™)	B.I.D. dosing Dual-acting agents Antihistamine, mast cell stabilizer, inhibitor of inflammatory mediators More effective at relieving symptoms than other classes of agents Longer duration of action Safe and effective for patients 3 years and older
Topical mast cell stabilizers	Safe and effective for allergic diseases affecting corneal changes	Cromolyn (Crolom) Lodoxamide (Alomide) Nedocromil (Alocril) Pemirolast (Alamast)	Cromolyn relives mild to moderate symptoms of vernal keratoconjunctivitis, vernal conjunctivitis, vernal keratitis Lodoxamide is highly potent
Topical antihistamines	Relieves signs and symptoms of pruritus and erythema	Levocabastine (Livostin) Emedastine (Emadine)	Dosing one to four times daily Safe and effective for patients 3 years and older
Topical NSAIDs	Relieves pruritus	Ketorolac (Acular)	Stinging and/or burning on instillation experienced up to 40% of patients
Tertiary			
Topical corticosteroids	Relieves all facets of the inflammatory response including erythema, edema, and pruritus	Loteprednol (Lotemax, Alrex) Rimexolone (Vexol) Fluorometholone (FML)	Appropriate for short-term use only Contraindicated in patients with viral infections
Immunotherapy	Identify and modulate allergen sensitivity		Adjunctive, although may be considered in secondary treatment in conjunction with allergic rhinitis
Ancillary			
Oral antihistamines	Mildly effective for pruritus	Loratadine Fexofenadine Cetirizine	May cause dry eyes and worsening of ocular symptoms (especially first generation) May not effectively resolve the ocular signs and symptoms of allergy
Topical cyclosporine	Treatment of the comorbid dry eye syndrome that occurs in the more persistent forms of ocular allergy	Restasis	Mild stinging on installation Effect not seen until 2–4 wk of treatment

OTC, over the counter; NSAIDs, nonsteroidal anti-inflammatory drugs

1. Avoidance is the primary foundation for allergy treatment.
2. Cold compresses provide considerable symptomatic relief, especially from ocular pruritus. This relief is most likely due to a decrease in neural stimulation.
3. All topical agents can be refrigerated to increase their soothing effect.
4. Lubrication with artificial tears can be applied topically two to four times a day as necessary.
5. Decongestants (vasoconstrictors) can be applied topically two to four times a day as necessary. Oxymetazoline has a faster onset of action, longer duration of action, and better decongestant effect than naphazoline and tetra-hydrozoline. However, chronic use for more than 5 to 7 days increases the development of conjunctivitis medicamentosa.
6. Topical antihistamines such as levocabastine (Livostin 0.05%) and emedastine (Emadine 0.05%) are selective H1-receptor antagonists for treating ocular pruritus. The levocabastine dosage for individuals 12 to 65 years old is one drop instilled in each eye,

twice daily. The dose may be increased to one drop three to four times daily. Levocabastine has been reported to be more effective than oral terfenadine for treatment of seasonal allergic conjunctivitis. Emedastine dosage is one drop in the affected eye up to four times daily while one drop of bepotastine (Bepreve 0.15%) is recommended for use twice a day and one to two drops of alcaftadine (Lastacaft 0.25%) are used once a day. OTC antihistamine eye drops such as Naphcon-A, Vasocon-A, and Opcon-A contain either pheniramine or antazoline along with a decongestant (e.g., naphazoline). These older antihistamines also have limited efficacy as their use for more than a few days can cause rebound congestion. Some topical antihistamines have been shown to have other anti-inflammatory effects and as such are considered **dual or multiple action agents**. Combined use of topical antihistamines and vasoconstricting agents is more effective than either agent alone for the relief of ocular itching.

7. Oral antihistamines are effective treatments of the ocular symptoms of allergic rhinoconjunctivitis, but some patients complain of the excessive drying effect that is common to the use of the first-generation oral antihistamines. Increasing the doses of certain later-generation oral antihistamines (nonsedat-ing) can have a similar effect. When prescribing topical agents for patients who continue to have symptoms despite being on oral antihistamines, one should consider discontinuing the oral agents as they can be contributing to the dry eye syndrome, in addition to allergen-induced conjunctivitis.

8. Topical mast cell stabilizers include cromolyn, lodoxamide, pemirolast, and nedocromil.

a. Cromolyn sodium 4% ophthalmic solution **(Crolom)** (OTC) can be applied four to six times a day with the dosage being decreased incrementally to twice a day as symptoms permit (pregnancy category B). Cromolyn sodium acts by inhibiting the release of histamine and leukotrienes from sensitized mast cells. It is used for prophylaxis of allergic and vernal keratoconjunctivitis in patients with moderate symptoms and may infrequently cause transient ocular burning and stinging. Clinically, it can stimulate pannus formation and increase healing in patients having corneal ulcers. In patients with the more chronic and severe forms of allergic conjunctivitis (i.e., vernal keratoconjunctivitis), cromolyn sodium improves keratitic epithelial defects.

b. Lodoxamide 0.1% (Alomide) is a mast cell stabilizer 2,500 times more potent than cromolyn. Lodoxamide inhibits antigen-induced histamine release, leukotriene formation, and eosinophil chemotaxis. Lodoxamide delivers greater and earlier relief than cromolyn sodium in patients and is used for prophylaxis of allergic and vernal keratoconjunc-tivitis. Lodoxamide 0.1% ophthalmic solution is applied topically in adults and children older than 2 years of age. The usual regimen is one to two drops to each eye four times a day for up to 3 months (pregnancy category B). The most common side effects are transient local irritation, burning, and itching.

c. Nedocromil 2% (Alocril) is a pyranoquinolone mast cell stabilizer that is used in the treatment of asthma and is indicated for the treatment of ocular pruritus. It relieves both the early- and late-phase symptoms of allergic conjunctivitis by inhibiting the release of histamine, decreasing chemotaxis, and inhibiting inflammatory cell actions (pregnancy category B).

d. Pemirolast 0.1% (Alamast), a pyridopyrimidine compound, is a mast cell stabilizer that is 100 times more potent than disodium cromoglycate. It is approved in Japan for use in the treatment of bronchial asthma, allergic rhinitis, and allergic/vernal conjunctivitis. The usual regimen is one to two drops to each eye four times a day.

9. Multiple action agents combine antihistamine and other anti-inflammatory activities involved in the allergic inflammatory cascade. Agents in this category include alcaftadine, azelastine, bepotastine, ketotifen, and olopatadine. All have H1-receptor blocking activity as well as mast cell stabilizing activity (Table 7-6)

Table 7-6 Ophthalmic Treatments for Ocular Allergy/Allergic Conjunctivitis

Topical Ophthalmic Agents Generic (Trade) Name	OTC/Rx [Conc] Bottle Size	Mechanism of Action	Dosage	Most Common Side Effects
Ketotifen (Alaway) (previously Rx Zaditor)	OTC 0.01%	Noncompetitive H1 receptor antagonist and mast cell stabilizer	≥3 y: 1 drop up to three times daily	Conjunctival injection, headache, rhinitis (10%–25%)
Cromolyn (Crolom)	OTC 4% 10 mL	Mast cell stabilizer	≥2 y: 1–2 drops up to four times daily	<4% irritation, burning, stinging eye, redness, and eye pruritus
Alcaftadine (Lastacaft)	Rx 0.25%	Noncompetitive H1 receptor antagonist and mast cell stabilizer	≥3 y: 1–2 drops once a day	<4% irritation, burning, stinging eye, redness, and eye pruritus
Bepotastine (Bepreve)	Rx 1.5% 10 mL	Selective H1 receptor antagonist and mast cell stabilizer	≥3 y: 1 drop twice daily	Taste (~25%) Headache, eye irritation, and nasopharyngitis in 2%–5%
Olopatadine (Pataday)	Rx 2% 2.5 mL	Selective H1-receptor antagonist and inhibitor of histamine release from mast cell	≥3 y: 1–2 drops once a day	Headache (7%)
Epinastine (Elestat)	Rx 0.05% 5 mL	Direct H1-receptor antagonist. Does not penetrate the blood brain barrier and therefore should not induce CNS side effects	≥3 y: 1 drop twice daily	Upper respiratory infection/cold symptoms (10%)
Olopatadine (Patanol)	Rx 0.1% 5 mL	Selective H1-receptor antagonist and inhibitor of histamine release from mast cell	≥3 y: 1–2 drops up to four times daily	Headache (7%)
Olopatadine (Pataday)	Rx 0.2% 2.5 mL	Selective H1-receptor antagonist and inhibitor of histamine release from mast cell	≥3 y: 1 drop 1× daily (first agent approved for 1× daily dosing)	Headache, stinging, blurred vision, nausea
Azelastine (Optivar)	Rx 0.15% 6 mL	Competes with H1-receptor sites on effector cells and inhibits release of histamine and other mediators involved in allergic response	≥3 y: 1 drop twice daily	Ocular burning (~30%), headache (~15%), bitter taste (~10%)
Emedastine difumarate (Emadine)	Rx 0.05%	Relatively selective histamine receptor antagonist	≥3 y: 1 drop up to four times daily	Headache (11%)
Levocabastine (Livostin)	Rx 0.1%	Selective H1-receptor antagonist	≥12 y: 1 drop up to four times daily	Ocular burning, stinging, itching (10%)
Lodoxamide tromethamine (Alomide)	Rx 0.1% 10 mL	Mast cell stabilizer	≥2 y: 1–2 drops up to four times daily	Ocular burning, stinging, itching (10%)
Nedcromil (Alocril)	Rx 2% 5 mL	Interferes with mast cell degranulation, especially release of leukotrienes and platelet activating factor	≥3 y: 1–2 drops twice daily	Headache (10%), bitter taste (10%), ocular burning (10%), nasal congestion (10%)
Pemirolast (Alamast)	Rx 0.1% 10 mL	Interferes with mast cell degranulation	≥3 y: 1 or 2 drops 4× daily	Can cause headache, dry eyes, runny nose. Can take up to 4 wk to take effect
Loteprednol etabonate (Lotemax) (Alrex)	Rx 0.5% 0.2%	Decreases inflammation by suppressing migration of polymorphonuclear leukocytes and reversing capillary permeability	≥3 y: 1–2 drops twice up to four times daily	Headache (10%), pharyngitis (10%), rhinitis (10%)
Ketorolac tromethamine (Acular)	Rx 0.5%	Pyrrolo-pyrrole NSAIDs, inhibits prostaglandin synthesis	≥12 y: 1 drop up to four times daily	Ocular burning, stinging, itching (10%)

H1, histamine 1; y, years old; CNS, central nervous system

a. Alcaftadine 0.25% (Lastacaft) effects mast cells, eosinophils, and various cytokines involved in the allergic response and is dosed at one drop in each eye once a day. Potential adverse effects include transient sting/ burn, headache, and flu-like symptoms (experienced by fewer than 4% of patients). It has demonstrated efficacy equivalent to olopatadine (Patanol) in a comparator study (pregnancy category B).

b. Azelastine 0.05% (Optivar) has a triple-action effect. It is an H1-receptor antagonist (antihistamine effect), stabilizes mast cells (mast cell stabilizing effect), and inhibits inflammation (anti-inflammatory effect). The dosage is twice a day because of the long duration of the drug's effectiveness (8 to 10 hours) in patients 3 years and older. The onset of action is within several minutes after application (pregnancy category C).

c. Bepotastine 1.5% (Bepreve) effects mast cells, eosinophils, and various cytokines involved in the allergic response. Bepotastine is dosed at one drop twice a day in each eye and binds H1 receptors with high affinity. Potential adverse effects include transient sting/burn, headache, and flu-like symptoms (experienced by <4% of patients (pregnancy category C).

d. Ketotifen 0.025% (Rx known as Zaditor) (OTC as Alaway) exerts several actions on the H1 receptor, the mast cell (stabilization), eosinophil chemotaxis, and adhesion molecule function. The recommended dosage for individuals 3 years and older is one drop in the affected eye every 8 to 12 hours (pregnancy category C).

e. Olopatadine 0.1% (Patanol) exerts multiple effects that include decreased H1-receptor binding, inhibition of mast cell mediator release (>90% *in vitro*), as well as on a variety of other inflammatory cells, for example, decreased eosinophilic infiltration. Olopatadine combined with oral loratadine produces greater relief of ocular itching than loratadine alone. With a $T_{1/2}$ of 3 hours, the usual dosage is one to two drops in each affected eye twice daily. Olopatadine can be administered to children as young as 3 years old and is well tolerated (pregnancy category C). Olopatadine 0.2% (Pataday) is a once-a-day formulation.

10. Nonsteroidal anti-inflammatory drugs (NSAIDs) administered orally, as well as topically applied cyclooxygenase inhibitors (e.g., 1% suprofen), are used in the treatment of vernal keratoconjunctivitis. Another topically applied NSAID (0.03% flurbiprofen) is used to treat allergic conjunctivitis and decreases conjunctival, ciliary, and episcleral hyperemia and ocular pruritus. Flurbiprofen (Ocufen), ketorolac (Acular), diclofenac (Voltaren), and bromfenac (Isday) are four topical nonsteroidal medications approved for the treatment of ocular conditions. Topical ocular NSAIDs, unlike topical corticosteroids, do not mask ocular infections, affect wound healing, increase intraocular pressure (IOP), or contribute to cataract formation. NSAIDs do cause low to moderate burning and stinging.

11. Topical ocular corticosteroids. When topically administered medications such as antihistamines, vasoconstrictors, dual (or multiple) acting agents, or cromolyn sodium are ineffective, low-potency topical steroids can be considered. "Modified" steroids, for example, loteprednol (Lotemax 0.5%; Alrex 0.2%) similar in concept to soft steroids are approved for the treatment of allergic conjunctivitis. They are commonly used in short courses (2 to 3 days up 1 to 2 weeks) to treat severe seasonal/intermittent or

perennial/persistent forms of allergic conjunctivitis. These drugs often are needed for long-term use in the more severe variants of chronic conjunctivitis (AKC, VKC, GPC). Topically or systemically administered steroids will produce a transient increase in IOP in genetically susceptible individuals (<5% of the general population). They have also been used for anterior uveitis. The use of the higher-potency or longer duration of the lower-potency agents must be done in consultation with an ophthalmologist.

a. Ocular corticosteroids should not be used in combination with an antibiotic. If an antibiotic is needed for an infection, concomitant use of an ocular steroid should only be undertaken in consultation with an ophthalmologist or other eye-care professional.

12. Treatment of ocular infections is based on differential diagnosis and types of discharge (Table 7-7). In adults, use an antibiotic with activity against *Staphylococcus* species, including *S. aureus* and *S. epidermidis*; *Streptococcus* species; and gram-negative organisms, primarily *Escherichia coli*, *Pseudomonas* species, and *Moraxella* species. Commonly used topical agents with a broad-spectrum antibiotic (without steroids) include azithromycin (1 drop twice a day for the first 2 days and then one drop daily for 3 to 7 days) or fluoroquinolones (that require more frequent daily administration, three to six times a day). In children, the choice focuses on an antibiotic that is effective against *S. pneumoniae*, *H. influenzae*, *Staphylococcus* species, and *Moraxella* species.

Table 7-7 Characterizations of Infectious Ocular Discharge and Differential Diagnosis

Type	Possible Causes	Nature of Discharge		
		Serous (watery)	Mucoid (stringy)	Mucopurulent
Allergic	Allergens: mold, dust, spores, pollen, etc.	+	+	
Bacterial	Most common: *Streptococcus*, *Staphylococcus*, *Haemophilus*, *Pseudomonas*, *Moraxella*		+	+
Hyperacute bacterial	*Neisseria gonorrhoeae*			+ (copious)
Viral	Adenovirus, herpes simplex, varicella-zoster	+	+	
Chlamydial	Chlamydia			+
Toxin	Dry cement mix, chemicals, etc.	+	+	+
Other	Dry eye, corneal abrasion, foreign body	+	+	+

13. Allergen immunotherapy is a well-established treatment for allergic conjunctivitis. Antigen-specific immunotherapy can reduce medication use and increased the dose of topically applied allergen needed to induce allergic symptoms of redness, pruritus, and swelling 10-to 100-fold.

14. Contact lens wear and topical medications. In general, it is best not to apply any medication to the eyes while wearing contact lenses. However, as long as the eyes are not injected, patients can either use their topical medications, but frequently dispose of their disposable contact lenses, or wait at least 10 minutes after instilling topical ocular

medication before inserting contact lenses.

VIII. WHEN OPHTHALMOLOGICAL CONSULTATION SHOULD BE OBTAINED

1. To evaluate any patient for the presence of cataracts and increased intraocular pressure, who is using ocular corticosteroids for more than 2 weeks.
2. Any persistent ocular complaint
3. Considering the use of a strong topical or systemic corticosteroid for treatment of an ophthalmic disorder

IX. ADVERSE REACTIONS TO OCULAR MEDICATIONS

1. Topical beta-adrenergic receptor antagonists are agents of choice for the treatment of glaucoma. Some topical beta-blockers include cardioselective agents (e.g., betaxolol) and nonselective agents (e.g., levobunolol, metipranolol, and timolol); the cardioselective agents cause less bronchospasm in asthmatic patients than the nonselective agents. However, all of the topical beta-blockers can produce respiratory symptoms in certain patients. Respiratory symptoms can develop even with minute quantities of topical beta-adrenergic blocker medications and are attributed to the higher serum concentrations of drug that result from bypassing hepatic degradation and directly entering the pulmonary vascular bed.
2. Intravenous fluorescein (i.e., fluorescein angiograms) is used to thoroughly examine the retinal and choroidal vasculature. Anaphylactoid reactions occur with an overall incidence of 5% increasing to as high as 50% for patients who report a previous history of reactions to fluorescein angiograms. The mortality rate is 1 per 220,000 fluorescein procedures (0.5% on initial exposure). Intravenous fluorescein reactions can cause nausea (2.9%), vomiting (1.2%), flushing and urticaria (0.2%), and systemic anaphylactoid reactions similar to those caused by hyperosmolar contrast media. Elevated plasma levels of histamine are found in patients receiving intravenous fluorescein. Because the reactions are not IgE mediated, immediate hypersensitivity skin testing in patients with prior history of intravenous fluorescein reactions is neither helpful nor predictive. Premedication protocols with H1- and H2-receptor blockers and prednisone are anecdotally helpful (see Chapter 10 for information on treatment for anaphylaxis).
3. **Preservatives**
   a. There are many adverse reactions associated with topical ophthalmic medications. Most of these reactions are toxic and result from chemical irritation. Only about 10% of all adverse reactions to topical ophthalmic drugs are truly allergic. The most common preservative is benzalkonium chloride, also known as BAC, which is a quaternary ammonium and a highly hydrosoluble bipolar compound with surfactant properties that are most commonly (8%) associated with irritant toxic reactions. The organomercurials (e.g., thimerosal) and the alcohols (e.g., chlorobutanol) have the highest association (20%) with allergic responses although the term allergy for the “alcohols” appears to be actually an irritant effect, whereas the organomercurials appear to truly interact with immune system as neoantigens. The salts of benzalkonium have been classified as being moderately

allergenic (4% to 11% skin test positive) whereas mercurial products are strongly allergenic (13% to 37% of skin tests are positive). True allergic sensitization by other preservatives (chlorhexidine and chlorobutanol) is unusual.

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8

Asthma Diagnosis

Stephen C. Lazarus

I. INTRODUCTION

Asthma is among the most prevalent chronic diseases in the United States and most of the developed world. Although the absence of a widely accepted definition of asthma makes it difficult to compare epidemiologic reports from different geographic regions, estimates suggest that there were 300 million people with asthma worldwide in 2010. Prevalence is greater in the United States than in developing countries, though the rate is increasing in both.

Asthma prevalence in the United States increased since the 1980s across all age, sex, and racial groups. The average prevalence in the United States in 2008 was 8.5%; in 2009, there were 250,000 deaths from asthma worldwide. In the United States, annual deaths from asthma increased from 2,598 in 1979 to 5,438 in 1998 before decreasing to 3,613 in 2006. Women account for 65% of all asthma deaths, and African Americans are three times more likely to die from asthma. The annual cost for asthma care is approximately $18 billion.

II. DEFINITION

Once thought of as a disease of abnormal airway smooth muscle with psychological overlay, the definition of asthma has changed with greater understanding of the inflammatory pathophysiology underlying the disease. There are too many mast cells, eosinophils, T lymphocytes, macrophages, and neutrophils in the airway epithelium and submucosa of people with asthma—even when their asthma is well controlled. This inflammation is linked causally to the nonspecific bronchial hyperresponsiveness that is ubiquitous in asthma. In addition, if the inflammation is not adequately treated, it leads in some patients to deposition of collagen in the subepithelial reticular layer ("remodeling") and fixed (nonreversible) airflow obstruction. In its 2010 update, the Global Initiative for Asthma (GINA) program describes asthma as follows:

> "Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment." (Global Strategy for Asthma Management and Prevention, used with permission from the Global Initiative for Asthma (GINA), http://www.ginasthma.org/)

This new definition, with its emphasis on inflammation, leads to increased emphasis on understanding and treating the airway inflammation that occurs in asthma.

III. CLINICAL FEATURES THAT DIAGNOSE ASTHMA

There is no one test that establishes the diagnosis of asthma. As a result, the diagnosis depends on clinical observations, including history, physical examination, and laboratory tests. Symptoms, physical findings, and laboratory results in asthma can overlap with other conditions (e.g., chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), vocal cord dysfunction), and at times the diagnosis of asthma cannot be confirmed until these other diagnoses are excluded. When the clinical features are straightforward, clinicians can make the diagnosis of asthma with minimal need for specific testing; when there is a question, pulmonary function tests and bronchoprovocation testing may be required.

IV. HISTORY

By definition, the clinical manifestations of asthma vary over time, and because of recall issues, many patients may not provide a classical description of asthma on their own. In addition, some symptoms are so nonspecific that patients attribute them to other conditions (e.g., age, smoking, infection, allergies). Targeted questioning can be revealing and should ask not only about wheezing and shortness of breath but also about cough, chest tightness, triggers, nocturnal symptoms, and prolonged coughing after "colds."

A. Common symptoms

The most common symptoms of asthma are recurrent chest tightness, wheezing, and cough. Shortness of breath is frequent. Approximately 80% of patients with asthma produce sputum at some point, often during the most severe part of an exacerbation or immediately thereafter. However, mucus hypersecretion and hypertrophy of mucus secretory cells (e.g., goblet cells, mucus glands) can occur in nonexacerbated asthma and are seen even in mild asthma. Asthma exacerbations are usually characterized by cough, wheezing, and dyspnea, but any one of these can predominate.

Chest tightness, wheezing, cough, and dyspnea are all manifestations of the change in airway caliber ("bronchoconstriction") that occurs in asthma. Wheezing results from turbulent flow through constricted airways, and cough usually results when stimulation of sensory nerves, found throughout the larger, central airways at bifurcations, occurs as a result of bron-choconstriction and mucosal folding. The pattern of symptoms can be an important variable and is often critical in differentiating asthma from other diseases that cause similar symptoms.

B. Symptoms with upper respiratory infections

Because patients with asthma have increased bronchial reactivity, anything that irritates the airway has the potential to cause bronchoconstriction. In addition, a number of respiratory viruses will increase bronchial reactivity, causing a significant shift in the dose–response to methacholine or histamine. Thus, many patients will report worsening of asthma symptoms that is triggered by respiratory infections, or cough, chest tightness, and wheezing that only occurs in the context of a respiratory infection.

C. Prolonged cough following an upper respiratory infection

Many patients with asthma are diagnosed after a number of years in which they report that routine respiratory viral infections "go to the chest," and that cough following a minor respiratory illness frequently persists for weeks to months. The diagnosis of asthma should

be entertained when these symptoms are elicited, and either empiric therapy or diagnostic testing for asthma (e.g., spirometry, bronchoprovocation) should be considered. Respiratory viral infections can increase bronchial reactivity within 2 to 3 days, and this hyperreactivity can last for up to several months.

D. Symptoms at night

Asthma symptoms at night are common yet frequently overlooked. Unless they dramatically interfere with sleep, many patients neglect to report them. Thus, clinicians should specifically ask about cough and wheeze at night. Nocturnal symptoms are likely due to a combination of diurnal variation in systemic cortisol and catecholamine levels, increased allergen levels in the bedroom, and gastroesophageal reflux. Studies using bron-choscopy with bronchoaleolar lavage and endobronchial biopsies demonstrate that increased airway inflammation peaks at about 4 a.m. Most deaths from asthma outside of hospitals occur at night, especially in the predawn hours.

E. Symptoms with exertion

Exercise-induced bronchoconstriction is a well-described entity (see below), but not all exercise-associated dyspnea is due to exercise-induced broncho-constriction. Individuals with preexisting obstructive or restrictive lung disease can develop dyspnea with exertion, without a change in lung function. Similarly, dyspnea with exertion can be a manifestation of deconditioning or cardiac disease.

F. Response to bronchodilator

The classic definition of asthma described bronchoconstriction that was variable and reversible either spontaneously or with bronchodilators, and most patients with asthma were expected to have normal or near-normal lung function between exacerbations. We now know that some asthmatics develop "remodeling" and that as a result their airflow obstruction may not reverse fully. Nevertheless, we expect that most asthmatics will demonstrate significant reversal of airflow obstruction with associated reduction in symptoms after aerosolized albuterol is administered. If the clinical picture highly suggests asthma, a clinical response to empiric bronchodilator treatment can confirm the diagnosis.

G. Cough variant asthma

In some patients with asthma, cough is the major, or *only*, symptom, and wheezing is absent. When this occurs, it is referred to as **cough variant asthma.** In these patients, baseline airway function is usually normal, but there is significant variability in peak expiratory flow or FEV_1, and there is heightened airway reactivity. Monitoring daily peak expiratory flow, or performing bronchoprovocation testing with methacholine, can be helpful in making this diagnosis.

H. Childhood versus adult onset

Although asthma may develop at any age, epidemiological studies show that onset of symptoms in childhood is more common. Twin studies suggest that early-onset asthma has a greater genetic component than does late-onset asthma. Asthma is more common in male children, perhaps because they have smaller airways and more atopy. In adults, asthma prevalence is greater in women, and the greater risk of adult-onset asthma in women is likely due, at least in part, to sex hormones.

V. RISK FACTORS

Numerous factors, including genetics, perinatal exposures, sex, atopy, respiratory infections, aeroallergens, tobacco smoke, and environmental pollutants, are all associated with the development of asthma. There is growing evidence that asthma is phenotypically heterogeneous, and different factors may be more important in different asthma phenotypes. Similarly, it is likely that different phenotypes are associated with different genotypes. Gene-by-gene and gene-by-environment interactions combine to determine asthma susceptibility and asthma phenotype. The "Asthma Predictive Index" identifies risk factors for the development of persistent asthma after the age of 5. Children younger than three who have had ≥4 episodes of wheezing in the previous year are significantly likely to develop persistent asthma if they have any of the following:

- A parental history of asthma
- A physician diagnosis of atopic dermatitis
- Evidence of sensitization to aeroallergens
- Two (or more) of the following:
  - Sensitization (antigen-specific IgE) to foods
  - ≥4% Eosinophilia
  - Wheezing (apart from respiratory viral infections)

The validity of this predictive index is being tested in many large cohorts and studies.

A. Family history and genetics

Asthma is more common in children whose parents have asthma, but a clearly heritable genetic component has not been identified. Inheritance of asthma does not follow a simple Mendelian pattern, suggesting that multiple genes are involved. Genes associated with atopy and production of IgE are localized to the long arm of chromosome 5, where genes associated with TH2 cytokines, the $beta_2$-adrenergic receptor, and with the development of airway hyperresponsiveness are also located. Despite these associations, specific asthma susceptibility genes have not been identified.

B. Environmental factors

Environmental exposures such as air pollutants and aeroallergens play an important role as triggers of asthma symptoms, but their role in the pathogenesis of asthma is less clear. Sensitization to common indoor allergens such as house dust mite, mold, and dog and cat dander is an independent risk factor for wheezing in young children; however, the link with development of asthma is tenuous. In fact, in some studies, children who were exposed to dogs or cats in the first years of life were actually protected against allergic sensitization and the development of asthma. Exposure to tobacco smoke *in utero* and in early infancy increases fourfold the risk of developing asthmalike symptoms (wheezing) in the first year of life. Both indoor (e.g., smoke from biomass fuels) and outdoor (e.g., smog) air pollutants are associated with asthma symptoms in patients with established disease, but their role as a cause of asthma has not been proven. Epidemiologic studies demonstrate a link between outdoor exercise in communities with high ambient ozone levels and the risk of asthma among school-age children. Occupational asthma is defined as asthma caused by an exposure to an agent encountered in the work environment. The list of agents is long and includes highly reactive molecules such as isocyanates (manufacture of plastics, automobile painting), irritants (detergent enzymes, disinfectants, manufacturing), and

immunogens. Frequently, workers are not aware of the specific chemicals to which they are exposed, and targeted questions may be required to uncover the nature of their work exposures (e.g., "Describe exactly what you do at work.") Also, office workers in factories may not realize that they share some exposures with the factory workers. Although most occupational asthma is immunologically mediated, a latency period of months to years is common.

C. Atopy and eczema

Atopy refers to the predilection to develop IgE-mediated responses to environmental allergens. It is identified by the presence of elevated serum IgE, peripheral blood eosinophilia, and skin test reactivity to specific allergens. Atopy is associated with asthma, allergic rhinitis, and atopic dermatitis (eczema). The latest revision of the National Heart Lung Blood Institute's *Guidelines for the Diagnosis and Management of Asthma (EPR3)* describes atopy as the strongest identifiable predisposing factor for developing asthma. Although this association is strong, the mechanisms by which atopy and asthma are linked are not well understood. As described above, genes associated with atopy colocalize with genes linked to TH2 differentiation and to bronchial hyperreactivity. Elevated IgE in young children is a risk factor for the subsequent diagnosis of asthma, and asthma prevalence is correlated with serum IgE levels and positive allergen skin tests.

D. Infection

The role of respiratory infections in the pathogenesis of asthma is unclear. Respiratory syncytial virus and parainfluenza virus are frequently associated with wheezing in infants, and approximately 40% of children hospitalized with respiratory syncytial virus infection will continue to wheeze or have asthma after age 7. In contrast to these data are those suggesting that respiratory infections early in life may actually provide protection against the development of asthma. The observation that asthma is less common in younger siblings, in children who attend group daycare, and in rural and underdeveloped communities has led to the "hygiene hypothesis" that suggests that childhood respiratory infections and/or regular exposure to endotoxin from farm animals may drive undifferentiated (null or TH0) T cells toward a TH1 and away from a TH2 phenotype (see Chapter 1). TH2 cells, defined by their cytokine profile (IL-3, IL-4, IL-5, GM-CSF), can be thought of as proallergic or proatopic and are found in increased numbers in the airways of asthmatics. There is a linear inverse relationship between the diversity of bacteria collected in bedroom dust and the prevalence of asthma in children.

VI. TRIGGERS

Asthma symptoms or exacerbations can be provoked by a number of triggers that can be either specific (e.g., specific allergens to which an individual is sensitized) or nonspecific (e.g., respiratory infection, air pollution). The initial history should solicit information about pets in the home, exposure to mold or dust, and occupational exposures. Although many patients can easily identify allergic triggers, others may require allergy skin tests to identify potential triggers. It is important to note that demonstrating allergen-specific sensitization does not prove that a given antigen is responsible for asthma symptoms. It can, however, suggest potential triggers and a strategy for avoidance. In addition, once sensitization has been identified, some patients recognize a link between exposure and

asthma symptoms. Many patients with asthma are sensitive to fumes, irritants, or changes in the weather. Cold dry air is often a trigger, and for some sensitized individuals, thunderstorms trigger asthma by releasing large amounts of respirable allergen fragments. Respiratory infections are a common trigger, especially those with rhinovirus and respiratory syncytial virus. Often, patients will provide a history of frequent "chest colds" and a cough that persists for weeks to months after a respiratory infection. These symptoms should suggest the possibility of asthma. Exercise is another common cause of worsening asthma. Nearly all patients with asthma will develop bronchoconstriction if they exercise to a sufficiently high level. However, for some patients, exercise may be the major or only trigger. Bronchoconstriction induced by exercise typically begins within 10 to 15 minutes after the cessation of exercise. Patients will often complain of chest tightness, cough, or wheezing and dyspnea.

VII. PHYSICAL FINDINGS

The classical finding in asthma is wheezing that occurs intermittently in association with cough or dyspnea. However, the differential for wheezing is long and includes asthma, COPD, heart failure, acute viral and bacterial bronchitis, tracheal stenosis, tracheobronchomalacia, vocal cord dysfunction, and anything that obstructs a conducting airway (e.g., tumor, foreign body). Constitutional symptoms are uncommon in asthma, except when a viral illness initiates an exacerbation or when the diagnosis is of a systemic disease associated with asthma, such as allergic bronchopulmonary aspergillosis (ABPA) or Churg-Strauss syndrome (CSS).

A. Wheezing

In most patients with asthma, symptoms are variable and intermittent and so are the physical findings. Between episodes, wheezing may be absent and the remainder of the physical examination may be completely normal. Wheezing is a manifestation of turbulent flow through narrowed airways and is most typically appreciated as high-pitched, musical sounds heard throughout the lung fields on expiration, especially at end-expiration. With more severe obstruction, wheezes may be heard during inspiration as well. In some patients, wheezing is heard only with forced expiration, and patients with **cough variant asthma** may never wheeze. In patients with very severe airflow obstruction, flow may be too low to produce a wheeze, and the chest may appear "quiet." Unfortunately, even very experienced clinicians cannot reliably predict the severity of airflow obstruction based on the presence, absence, or quality of wheezing, and measurement of lung function is required to quantify airflow obstruction. Wheezing may also result from focal narrowing of proximal bronchi, the trachea, or the larynx and subglottic region. Although these sounds are frequently transmitted through the lungs, they are typically loudest over the area of narrowing and are heard as a monophasic (nonmusical) wheeze that often begins and ends at the same point in the respiratory cycle. Focal narrowing that is inside the thorax will be worse during exhalation; that outside the thoracic outlet will be worse with inhalation, often resulting in **inspiratory stridor.** The presence of musical wheezes in the context of intermittent cough, dyspnea, and shortness of breath strongly suggests asthma. Atypical wheezing or an atypical

history should lead to further investigation.

B. Prolonged expiratory phase

During normal breathing at rest, the ratio of the time required to complete inspiration to that required for expiration (the I:E ratio) ratio is approximately 1:2. As airway narrowing occurs during an asthma exacerbation, expiratory airflow decreases and the time required for exhalation is greater. The I:E ratio may decrease substantially, sometimes to 1:4 or 1:6. Prolongation of the expiratory phase is often obvious on physical examination, and the greater the prolongation, the more severe the obstruction. Although studies have confirmed that clinicians can accurately predict FEV_1 only about one-third of the time, a forced expiratory time (the time required to completely empty the lungs from total lung capacity) >6 seconds suggests that the FEV_1/Forced vital capacity (FVC) ratio is <0.50.

C. Accessory muscles of respiration

As airway narrowing becomes more severe, the resistance to airflow increases, as does the work of breathing. To help overcome this, patients with severe asthma often rely on the sternocleidomastoid and intercostal muscles and may assume an upright seated position with the arms or elbows resting on an adjacent surface to support the upper chest. This so-called tripod position facilitates recruitment of accessory muscles and also allows for upward displacement of flattened diaphragms, which improves diaphragmatic function by optimizing the length–tension relationship of the muscle.

D. Pulsus paradoxus

Pulsus paradoxus is an exaggeration of normal physiology, defined as a decrease in systolic arterial pressure of >10 mm Hg during inspiration. A drop of >25 mm Hg reflects severe airflow obstruction. Pulsus paradoxus results from both the direct transmission to the pulmonary vascular tree of large intrathoracic pressure swings and to a decrease in left ventricular stroke volume.

E. Allergic manifestations

Increased nasal secretions and mucosal edema suggest allergic rhinitis. Together with the skin findings of eczema, these are signs of atopy, which is closely linked to asthma. Nasal polyps can be seen in allergic rhinitis but should suggest “triad asthma” or “Samter’s triad”: asthma, nasal polyps, aspirin sensitivity. The finding of nasal polyps in a child with respiratory symptoms should raise the possibility of cystic fibrosis since triad asthma is uncommon in children.

F. Signs of severe asthma

All of the findings described above can be seen in severe asthma, but certain physical findings should be considered warning signs of severe and potentially life-threatening asthma. These include tachycardia (heart rate >120), tachypnea (respiratory rate >30), pulsus paradoxus, evidence of a hyperinflated chest, cyanosis, drowsiness, and difficulty speaking. In addition, a quiet chest in a symptomatic asthmatic is of grave concern.

VIII. ROUTINE LABORATORY FINDINGS

A. Blood tests

There are no abnormalities in CBC or blood chemistries that are specific for asthma, and these tests should not be routine in all patients. The peripheral white blood cell count can be elevated with concomitant infection, and patients with hypocarbia from a prolonged exacerbation may demonstrate renal bicarbonate wasting. An elevated peripheral blood eosinophil percentage may be seen in allergic asthma but is not specific for asthma nor as helpful in discriminating between asthma phenotypes as is sputum eosinophilia. The latter can be important in guiding corticosteroid therapy, and persistent sputum eosinophila despite corticosteroids identifies a group with lower lung function and poorer asthma control. Persistently high blood eosinophil percentages (>15%) should suggest a diagnosis other than asthma (e.g., parasitic infection, CSS). Elevated serum total IgE suggests allergic disease, and IgE levels >1,000 IU/mL are sometimes seen in ABPA.

B. Respiratory secretions

Chronic mucus hypersecretion occurs in 10% to 50% of asthmatics, and classical descriptions of asthma reported the presence of mucus plugs and eosinophils in the sputum, as well as Curschmann's spirals and Charcot-Leyden crystals. These reports, from the 1800s era of Curschmann, Charcot, Leyden, and Osler, arose from careful examination of expectorated sputum. Patients often report the presence of plugs or casts in their sputum, and these can frequently be visualized with the naked eye. **Curschmann's spirals** are very small, mucinous fibrils that are thought to represent bronchiolar plugs. **Charcot-Leyden crystals** are condensation products of eosinophil major basic protein and are seen whenever there is a high turnover of eosinophils. In the modern era, clinicians infrequently examine sputum, but plugs, spirals, and crystals are sometimes identified on sputum samples submitted for microbacterial or cytological studies, and their presence should suggest the diagnosis of asthma.

C. Radiographs

There are no radiographic findings that are specific for asthma, and thus neither plain chest radiographs nor computed tomography (CT) of the chest is recommended routinely. The plain chest radiograph is usually normal in asthma or can demonstrate flattening of the diaphragms due to hyperinflation. The major value of radiographs is to exclude other diagnoses. A plain chest radiograph can be useful in ruling out pneumonia, CHF, and mass lesions that can cause focal wheezing. CT scans can demonstrate bronchiectasis and mucus plugging, suggesting ABPA, or patchy or diffuse infiltrates that might suggest eosinophilic pneumonia, CSS, or other causes of wheezing.

D. Measures of oxygenation

Arterial blood gas analysis should not be done routinely, for significant gas exchange abnormalities usually do not exist until airflow obstruction becomes severe. However, measurement of arterial blood gases should be performed in any patient with obvious severe obstruction or who is markedly tachypneic. Patients with mild-to-moderate obstruction will usually have a normal P_aO_2 and a normal or slightly low P_aCO_2. As airflow obstruction worsens, the P_aO_2 falls, and this decrease is linearly related to the severity of the obstruction. Typically, patients with severe acute asthma will hyperventilate at first and maintain a relatively normal P_aO_2; the P_aCO_2, accordingly, will be low. As the

airflow obstruction, mucosal edema, and mucus plugging worsen, so do ventilation–perfusion relationships, and the P_aCO_2 begins to increase. **Thus, even a normal P_aCO_2 should alert the clinician to the potential for impending respiratory failure.** Measurements of S_aO_2 alone can provide a false sense of security in patients with severe asthma as they provide no insight into P_aCO_2. However, when combined with vital signs and clinical assessment, monitoring of S_aO_2 is generally adequate. In patients with tachypnea, tachycardia, and use of accessory muscles of respiration, or with obvious fatigue or altered level of consciousness, arterial blood gases should be assessed.

IX. PULMONARY FUNCTION TESTS

Because airflow obstruction is one of the criteria for the diagnosis of asthma, some measure of airway function is required. Both the National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3 and the GINA recommend the use of spirometry, which records the volume of air exhaled (after a full inhalation to total lung capacity) plotted against time. This is a good screening test for obstructive and restrictive lung disease. Multiple devices for making these measurements are available that are inexpensive and that meet technical criteria recommended by the American Thoracic Society. When the volume inhaled or exhaled is plotted against flow rather than time, the result is a **flow–volume curve,** which provides the same numerical values as spirometry, but also a visual representation of the maneuver, which aids in interpretation.

A. Performing pulmonary function tests

Although the devices for obtaining spirometry and flow–volume curves are relatively inexpensive and easy to use, reliable results require well-trained technicians who can perform the test correctly and who can make sure that the patient understands the maneuver and provides a maximal effort.

B. Spirometry

Guidelines recommend that spirometry be performed before and after administration of an aerosolized bronchodilator in all patients suspected of having asthma. The two parameters most commonly evaluated are the forced expiratory volume in 1 second (FEV_1) and FVC (Fig. 8-1). The FEV_1 measures both the volume generated early in the forced expiratory maneuver, which is highly effort dependent, and some of the midportion of the exhaled volume, which is effort independent. As a result, it is reproducible and sensitive for diagnostic purposes. The FVC is the total volume of air exhaled from maximum inhalation to total lung capacity (TLC) until no more air can be expelled (Residual Volume, RV). This measurement requires considerable patient effort and is usually dependent on skilled coaching by the technician. Airflow obstruction is defined as a reduction in the ratio of FEV_1 to FVC (absolute value) and in the FEV_1 (as a percentage of predicted) (Table 8-1). Predicted values are based on age, height, sex, and ethnicity and should be validated for the population served by a given laboratory. For the diagnosis of asthma, spirometry is usually performed before and after the administration of 2 to 4 puffs of short-acting bronchodilator, such as albuterol. Reversibility is defined as an increase after bronchodilator of 12% and ≥200 mL in FEV_1 or FVC. It is

important to note that failure of a patient to demonstrate reversibility after administration of a bronchodilator on a single occasion does not mean that he or she will not respond to more aggressive treatment, and patients with significant obstruction in whom the clinical diagnosis of asthma seems likely should be retested after a course of inhaled or oral corticosteroids. Another measurement that can be obtained from spirometry is the $FEF_{25\%–75\%}$ (also known as the maximum mid-expiratory flow rate, MMEFR). This represents the average forced expiratory airflow between 25% and 75% of the expired vital capacity (VC). This is the most effort-independent portion of the expiratory maneuver and is believed to be the most sensitive to changes in airflow in the small, peripheral airways.

Table 8-1 Patterns of Pulmonary Function in Asthma

Patterns of Pulmonary Function in Asthma	
FEV_1 (forced expiratory volume in 1 s)	Reduced
FVC (forced vital capacity)	Reduced or normal
FEV_1/FVC	Reduced
PEF (peak expiratory flow)	Reduced
$FEF_{25\%–75\%}$ (maximal mid-expiratory flow)	Reduced
Flow–volume curve	Curvilinear
TLC (total lung capacity)	Normal or increased
DL_{CO} (diffusing capacity for carbon monoxide)	Normal or increased

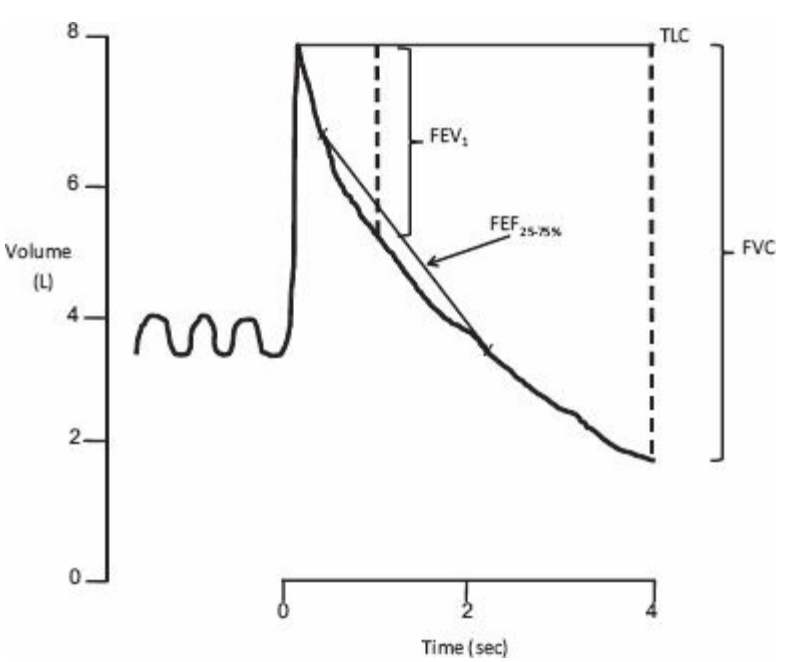

Figure 8-1. Spirogram is performed by having subject breathe quietly, and then inhale maximally to total lung capacity, followed by exhaling completely as rapidly and forcefully as possible. FEV_1, forced expiratory volume in 1 second; $FEF_{25\%–75\%}$, forced mid-expiratory flow rate; FVC, forced vital capacity; TLC, total lung capacity.

C. Flow–volume curve

Most modern instruments, including small handheld spirometers, also produce a graphic plot of flow versus lung volume, the flow–volume curve **(Fig. 8-2A,B).** This shows both the maximal inspiratory and expiratory flows and the relationship of tidal breathing to maximal flow. In the healthy individual, the expiratory limb of the curve declines linearly and has a slope of approximately 45 degrees. On the inspiratory limb, flow increases to a peak at the midpoint of inhalation before decreasing symmetrically as the lung volume approaches TLC. The flow–volume curve allows for visualization (and quantification) of flows at all lung

volumes. Often, in mild (or early) disease, expiratory flow rates decrease at lower lung volumes, resulting in a curvilinear expiratory limb, despite a normal FEV_1 and FEV_1/ FVC. This occurs because lung elastic recoil which helps "tether" airways open decreases at lower lung volumes, when the lung is distended less. Peak flow can also be obtained from the flow–volume curve; however, because of odd convention, the peak flow is usually reported as liters per second (LPS) on the flow–volume curve, whereas handheld peak flow meters typically report flow as liters per minute (LPM). Multiplying the former by 60 allows patients to compare their values measured at home with those in the laboratory and provides "calibration" of their devices.

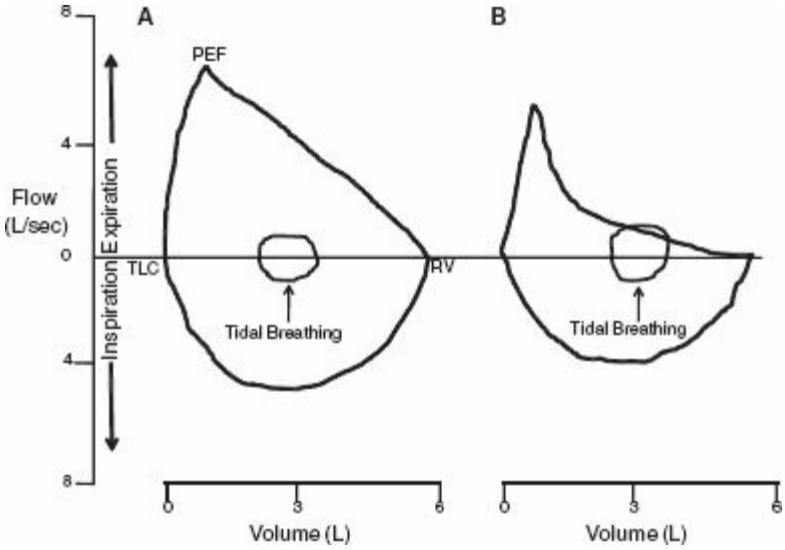

Figure 8-2. The flow–volume loop is constructed by plotting inspiratory and expiratory flow (on the vertical axis) against inspired and expired volume (on the horizontal axis). The patient first breathes quietly, and tidal volume loops are recorded. Next the patient breathes in as hard and fast as possible to TLC, then breathes out completely as hard and fast as possible. **A:** A normal flow–volume curve in which expiratory flow decreases linearly as lung volume decreases. **B:** Obstructive lung disease, with a curvilinear expiratory limb reflecting decreased maximal expiratory flow at all lung volumes.

D. Peak flow

Peak flow is defined as the maximum airflow during a forced expiration beginning with the lungs fully inflated and is usually achieved within ≤0.1 second. This is a very effort-dependent maneuver, and the variability of the measurement is significantly greater than for measurement of FEV_1. For this reason, **guidelines prefer spirometry over peak flow for the *diagnosis* of asthma.** The major advantage of peak flow, however, is the ease and frequency with which it can be measured at home, which makes it useful for ***monitoring*** asthma control. In normal individuals, the diurnal variability in peak flow is <20%; in asthma, diurnal variability of ≥20% is considered by many to reflect bronchial hyperresponsiveness. In patients with normal spirometry, demonstration of diurnal variability ≥20% over 1 to 2 weeks suggests a diagnosis of asthma. Long-term peak flow monitoring can be useful in patients who have moderate and severe persistent asthma and a history of severe exacerbations and those who have poor perception of deteriorating asthma control. In addition, measurement of peak flow at home during exacerbations can provide patients and their health care providers insight into the severity of the exacerbation. Because of the variability of peak flow measurements, devices, and predicted values, the most valuable comparison is with the patient's own "personal best" using the same device.

E. Airway resistance

Airway resistance is easy to measure using a body plethysmograph. It requires a skilled technician and patient cooperation but is not effort-dependent like spirometry. Airway resistance measurements are more sensitive than spirometry in measuring subtle changes in airway smooth muscle tone and are not affected by effort or by volume history as is FEV_1.

F. Lung volumes

TLC and VC are usually normal in asthma. However, with moderate-to-severe obstruction, increased transmural pressure causes airway closure and an increase in residual volume due to trapped gas. As a result, FVC can be reduced in severe asthma. A "slow VC" may demonstrate a larger volume than the FVC maneuver. In the presence of airflow obstruction on spirometry, a reduction in FVC may be due to air trapping or to concomitant restrictive lung disease. Measurement of TLC, preferably by plethysmography, will confirm or exclude restriction. When obstruction is severe, the TLC measured by single-breath gas dilution can significantly underestimate TLC. The difference between this volume and the TLC measured plethys-mographically represents trapped gas.

G. Diffusing capacity

The diffusing capacity for carbon monoxide (D_{LCO}), usually measured by a single breath technique, reflects **pulmonary capillary blood volume** and is usually normal in asthma. Occasionally, the D_{LCO} is elevated in asthma, perhaps because the more negative pleural pressure swings that occur as a consequence of bronchial narrowing increase perfusion of the apices of the lungs. Airflow obstruction accompanied by a low D_{LCO} suggests emphysema.

H. Bronchoprovocation testing

When asthma is suspected and spirometry is normal, bronchoprovocation testing may help confirm the diagnosis. Bronchial hyperresponsiveness (BHR), an exaggerated response to a variety of nonspecific stimuli, is a ubiquitous finding in asthma. The test can examine the response to direct stimuli such as methacholine or histamine or to indirect stimuli such as exercise, eucapneic hyperventilation, hypertonic saline, adenosine mono-phosphate (AMP), or mannitol. Historically, histamine and methacholine have been used most commonly, and these agents have good correlation and reproducibility. The test is performed by administering a saline control aerosol, followed by incrementally increasing concentrations of the stimulus, until a predetermined endpoint is reached. Most laboratories report the concentration of agonist required to achieve a 20% decrease in FEV_1 (the provocative concentration or PC_{20}). The concentration required to decrease specific airway conductance by 40% can be a more sensitive endpoint. The lower the PC_{20}, the greater the degree of bronchial hyperre-sponsiveness, and patients with asthma will usually have a PC_{20} $\leq$8 mg/mL. **Bronchoprovocation testing has a strong negative predictive value, and a negative test effectively rules out asthma.** However, specificity is not so high, and BHR is seen in patients with cystic fibrosis, COPD, and allergic rhinitis. Indirect tests of BHR assess the presence of airway inflammation as well as the presence of BHR and may be more sensitive than methacholine. Exercise testing is difficult to standardize outside of laboratories that perform many tests. Mannitol is approved by the FDA and is packaged as easy-to-use single-use kits.

X. MARKERS OF INFLAMMATION

Eosinophils, neutrophils, eosinophil cationic protein, and tryptase in sputum, exhaled nitric oxide (F_ENO), various volatile substances collected from exhaled breath condensate (EBC), and airway biopsies have all been tested as biomarkers for the diagnosis and monitoring of asthma. Although some are promising, only F_ENO is currently feasible outside of research laboratories. F_ENO is elevated in asthmatics not taking corticosteroids and can be used as a marker of adherence to steroids as well as a guide to management, but elevated F_ENO is not specific for asthma.

XI. DIFFERENTIAL DIAGNOSIS

Cough, wheezing, and shortness of breath are seen in a number of respiratory diseases in addition to asthma, and many of these are associated with airflow obstruction on spirometry. In fact, there is no one sign or symptom that is unique to asthma. When symptoms are episodic and recur frequently, with asymptomatic periods in between, the diagnosis of asthma may be obvious. However, rhinosinusitis, postnasal drip, bronchitis, bronchiectasis, vocal cord dysfunction, CHF, and gastroesophageal reflux disease (GERD) may all present with intermittent symptoms similar to asthma (Table 8-2). A careful history and physical examination, and spirometry, will usually confirm a diagnosis of asthma. Sometimes, bronchoprovocation testing, as well as tests to exclude other diseases (e.g., GERD, CHF), are required.

Table 8-2 Common Causes of Wheezing

Lower Respiratory Tract	Upper Respiratory Tract	Nonairway Diseases
Asthma	Rhinosinusitis	Pulmonary edema
COPD	Postnasal drip syndrome	Congestive heart failure
Bronchiectasis	Paradoxical vocal cord movement	Aspiration
Cystic fibrosis	Vocal cord paralysis, tumor	Parasitic infection
Pulmonary embolism	Subglottic stenosis	
Lymphangitic spread of cancer	Tracheo- or bronchomalacia	
	Foreign body	

A. Distinguishing asthma from COPD

Asthma and COPD share many features, and differentiating between them can be difficult. Classically, airflow obstruction in asthma was thought to be fully reversible, while COPD was characterized as airflow limitation that is not fully reversible and that is usually progressive. However, some asthmatics develop fixed obstruction ("remodeling,") and many patients with COPD have a significant response to bronchodilators. Age of onset, smoking history, nocturnal symptoms, and variability in symptoms can help the clinician distinguish between asthma and COPD (Table 8-3), although it is important to recognize that these diagnoses are not mutually exclusive.

Table 8-3 Clinical Features Differentiating COPD and Asthma

	COPD	Asthma
Smoker or ex-smoker	Nearly all	Possibly
Symptoms under age 35	Rare	Often
Chronic productive cough	Common	Uncommon
Breathlessness	Persistent and progressive	Variable
Night time waking with breathlessness and/or wheeze	Uncommon	Common
Significant diurnal or day-to-day variability of symptoms	Uncommon	Common

(Reproduced from the National Clinical Guideline Centre. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. London: National Clinical Guideline Centre, 2010. Available from: http://guidance.nice.org.uk/%20CG101/Guidance/pdf/English, with permission.)

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9

Asthma Treatment

Joel M. Hartman, Jason W. Caldwell, Rodolfo M. Pascual, and Stephen P. Peters

I. GENERAL PRINCIPLES OF TREATMENT

A. Asthma heterogeneity

There is considerable heterogeneity with respect to clinical presentation, severity, natural history, response to therapy, and pathogenetic factors among patients with asthma. Asthma should be considered as a syndrome rather than a single entity because it probably consists of multiple disorders having common clinical manifestations. Response to asthma therapy is also variable, underscoring the importance of ongoing follow-up and evaluation to assess impairment and disease control.

B. Main components of therapy

Recent Expert Panel Reports and practice guidelines have anchored effective asthma care to four key components:

1. Assessment and monitoring of severity and control
2. Control of environmental factors and comorbid conditions
3. Partnering with patients and families
4. Pharmacologic therapy

C. Asthma severity and control as the basis for treatment

1. Severity versus control. Ongoing assessment and monitoring are integral to achieving adequate disease control and minimizing functional limitations from the disease. Appropriate patient surveillance is linked to two key concepts: severity and control. Severity is defined as the intrinsic intensity of the disease process, whereas control is defined by the degree to which asthma manifestations are minimized and goals of therapy are met. Asthma severity is assessed and used to guide appropriate decision making with regard to medication choices and other therapeutic interventions. Although assessing severity is most accurate in patients prior to starting therapy, many patients present on preexisting regimens to a new health care provider. Once medication is initiated, the focus shifts to the assessment of control, guiding decisions regarding medication maintenance and adjustment.

2. Impairment versus risk. Both asthma severity and control include the domains of impairment and risk. Impairment encompasses symptom intensity and the resultant functional limitations. While evaluation of impairment can usually be elicited by careful history, questionnaires (e.g., Asthma Control Test) have been developed to help standardize the assessment of impairment. The risk domain encompasses the likelihood of exacerbations, decline in lung function, reduced growth in children, and risk of adverse medication effect. The test most used to evaluate the risk domain is spirometry Particularly important in risk assessment is the use of the forced expiratory volume in 1 second (FEV1) expressed as a percent of the predicted value or as a proportion of the forced vital capacity (FVC) or

FEV_1/FVC. Regardless of the methods used for assessment, both impairment and risk are key domains in the evaluation of asthma severity and control.

D. Objectives of treatment

With regard to treatment, objectives for the short term include the immediate relief of symptoms and airflow obstruction. Long-term objectives include preventing chronic and troublesome symptoms; the maintenance of as "normal" pulmonary function as possible; maintaining normal activity levels; preventing exacerbations, emergency department visits, and hos-pitalizations; minimizing the side effects of medications; and meeting the patient's and family's expectations for asthma treatment.

E. Stepped care. Current guidelines emphasize classifying asthma severity as intermittent or persistent; persistent asthma is further categorized as mild, moderate, or severe. In practice, the emphasis is on assessment of asthma severity prior to initiating therapy with future assessment of control for monitoring and adjusting therapy. Patients at any level of impairment may have severe exacerbations, usually due to infections or airborne exposures (e.g., allergens, irritants). It is for this reason that recent guidelines modified the designation of "mild intermittent asthma" to become "intermittent asthma," acknowledging that a patient at any level of severity can have severe exacerbations.

Tables 9-1 and 9-2 summarize an overview of the pharmacology of asthma therapy as outlined by NAEPP Expert Panel Report according to asthma phenotype classification. In order to avoid unnecessary long-term medication side effects, the minimal amount of medication that is required to provide control of inflammation, symptoms, and airflow limitation should be used. The key principle is that severe asthma requires aggressive pharmacological therapy, whereas mild or improving asthma requires less medication, and therapy should be stepped-up and stepped-down accordingly. In newly diagnosed symptomatic asthmatics, it is often recommended that asthma therapy begin at one step higher than the patient's current status, followed by a cautious reduction in therapy once the patient is clinically stable. With regard to categorization of asthma severity, it should be based on the lowest level of treatment required to maintain control.

Table 9-1 Stepwise Approach for Managing Asthma in Patients ≥12 Years of Age

Intermittent Asthma	Persistent Asthma: Daily Medication (Step Up or Down Based on Assessment of Control)				
Step 1 ***Preferred:*** SABA prn	**Step 2** ***Preferred:*** Low-dose ICS ***Alternative:*** LTRA, nedocromil, or theophylline	**Step 3** ***Preferred:*** Low-dose ICS + LABA or medium-dose ICS ***Alternative:*** Low-dose ICS + either LTRA, theophylline, or Zileuton	**Step 4** ***Preferred:*** Medium-dose ICS + LABA ***Alternative:*** Medium-dose ICS + either LTRA, theophylline, or zileuton	**Step 5** ***Preferred:*** High-dose ICS + LABA *and* Consider omalizumab for patients with allergic asthma	**Step 6** ***Preferred:*** High-dose ICS + LABA + oral corticosteroid *and* Consider omalizumab for patients with allergic asthma
At each step: Patient education, environmental control, and management of comorbidities					

(Reproduced from National Heart, Blood, and Lung Institute Expert Panel Report 3 (EPR 3): Guidelines for the Diagnosis and Management of Asthma. NIH Publication no. 08-4051, 2007.)

Table 9-2 Long-Term Controller Medications

Name/Products	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues
Corticosteroids	*Indications*	Cough, dysphonia, oral thrush	Spacer/holding chamber devices with nonbreath-activated MDIs and mouth washing after inhalation decrease local side effects.
Inhaled (ICS):	Long-term prevention of symptoms; suppression, control, and reversal of inflammation	In high doses, systemic effects may occur (e.g., adrenal suppression, osteoporosis, skin thinning, easy bruising).	Preparations not absolutely interchangeable on a mcg or per puff basis
Beclomethasone dipropionate	Reduce need for oral steroid	In low to medium doses, suppression of growth velocity in children, but this effect might be transient (clinical significance has not been established).	Risks of uncontrolled asthma should be weighed against the limited risks of ICS therapy.
Budesonide	*Mechanisms*		"Adjustable dose" approach to treatment may enable reduction in cumulative dose of ICS treatment over time without sacrificing maintenance of asthma control.
Ciclesonide	Block late reaction to allergen and reduce BHR		Dexamethasone is not included as an ICS for long-term control because it is highly absorbed and has long-term suppressive side effects.
Flunisolide	Inhibit cytokine production, adhesion protein activation, and inflammatory cell migration and activation		
Fluticasone propionate	Reverse beta$_2$ receptor downregulation Inhibit microvascular leakage		
Mometasone furoate			
Triamcinolone acetonide			
Systemic:	*Indications*	Short-term use: reversible abnormalities in glucose metabolism, increased appetite, fluid retention, weight gain, mood alteration, hypertension, peptic ulcer, and rarely aseptic necrosis	Use at lowest effective dose. For long-term use, alternate-day am dosing produces the least toxicity.
Methylprednisolone	Short-term (3–10 d) "burst": to gain prompt control of inadequately controlled persistent asthma	Long-term use: adrenal axis suppression, growth suppression, dermal thinning, hypertension, diabetes, Cushing's syndrome, cataracts, muscle weakness, and—in rare instances—impaired immune function	
Prednisolone	Long-term prevention of symptoms in severe persistent asthma: suppression, control, and reversal of inflammation	Consideration should be given to coexisting conditions that could be worsened.	
Prednisone	*Mechanisms*		
	Same as inhaled		
Immunomodulators	*Indications*	Pain and bruising of injection sites in 15%–20% of patients	Monitor patients following injection. Be prepared to identify and treat anaphylaxis that may occur.
Omalizumab (anti-IgE) for subcutaneous use	Long-term control and prevention of symptoms in adults (≥12 y) with moderate to severe persistent allergic asthma inadequately controlled on ICS	Anaphylaxis reported	Dose is administered every 2–4 wk and is dependent on body weight and IgE level before therapy.
		Malignant neoplasms reported in 0.5% of patients compared to 0.2% receiving placebo; relationship to drug is unclear.	
	Mechanisms		A maximum of 150 mg can be given in one injection.
	Binds circulating IgE preventing it from binding to FcεR1 receptors on basophils and mast cells		Needs to be stored under refrigeration at 2°C–8°C
	Decreases mast cell mediator release from allergen exposure		Whether patients will develop significant antibody titers with long-term use is unknown.
	Decreases the number of Fc ε R1s in basophils and submucosal cells		
Leukotriene receptor antagonists (LTRAs)	*Mechanisms*		May attenuate EIB in some patients
	Selective competitive inhibitor of CysLT$_1$ receptor		Do not use LTRA + LABA as a substitute for ICS + LABA.
Montelukast tablets and granules	*Indications*	No specific adverse effects have been identified	A flat dose-response curve, without further benefit, if dose is increased above those recommended
	Long-term control and prevention of symptoms in mild persistent asthma for patients ≥1 y. May be used in combination with ICS as combination therapy in moderate persistent asthma	Rare cases of Churg-Strauss have occurred but the association is unclear	Administration with meals decreases bioavailability; take at least 1 h before or 2 h after meals.
			Zafirlukast is a microsomal P450 inhibitor that can inhibit metabolism of warfarin. Monitor INR during administration.
Zafirlukast tablets	*Indications*	Postmarketing surveillance has reported cases of reversible hepatitis and, rarely, irreversible hepatic failure resulting in death and liver transplant.	Patients should be warned to discontinue if they experience signs and symptoms of liver dysfunction, and patients' LFTs should be monitored.
	Long-term control and prevention of symptoms in mild persistent asthma for patients ≥7 y. May also be used with ICS as combination therapy in moderate persistent asthma		
5-Lipoxygenase inhibitor	*Mechanisms*	Elevation of liver enzymes reported. Limited case reports of reversible	Microsomal P450 inhibitor that can inhibit the metabolism of warfarin
	Inhibits the production of LTs from		

Zileuton tablets	arachidonic acid, both LTB_4 and the cysteinyl leukotrienes *Indications* Long-term control and prevention of symptoms in mild persistent asthma for patients ≥12 y May be used with ICS as combination therapy in moderate persistent asthma	hepatitis and hyperbilirubinemia	and theophylline. Monitor hepatic enzymes (ALT).
Long-acting $beta_2$-agonists (LABAs) *Inhaled LABA:* Formoterol Salmeterol *Oral:* Albuterol, sustained-release	*Indications* Long-term prevention of symptoms, added to ICS Prevention of EIB Not to be used to treat acute symptoms or exacerbations. *Mechanisms* Smooth muscle relaxation following adenylate cyclase activation and increase in cyclic AMP, producing function antagonism of bronchoconstriction Compared to SABA, salmeterol (but not formoterol) has a slower onset of action. Both salmeterol and formoterol have longer duration of action (>12 h) compared to SABA.	Tachycardia, skeletal muscle tremor, hypokalemia, QTc prolongation in overdose A diminished bronchoprotective effect may occur within 1 wk of chronic therapy. Clinical significance has not been established. Potential risk of uncommon, severe, life-threatening or fatal exacerbation	Not to be used to treat acute symptoms or exacerbations Should not be used as monotherapy for long-term control of asthma or as anti-inflammatory therapy May provide more effective symptom control when added to standard doses of ICS compared to increasing ICS dosage Clinical significance of potentially developing tolerance is uncertain. Decreased duration of protection against EIB may occur with regular use. Inhaled route preferred because LABAs are longer acting and have fewer side effects than oral sustained-release agents.
Quick-relief medications			
Short-acting $beta_2$-agonists (SABAs) *Inhaled SABA:* Albuterol Levalbuterol Pirbuterol	*Indications* Relief of acute symptoms Preventative treatment for EIB prior to exercise *Mechanisms* Binds to beta-2 adrenergic receptor, producing smooth muscle relaxation following adenylate cyclase activation and increase in cyclic AMP producing functional antagonism of bronchoconstriction	Tachycardia, skeletal muscle tremor, hypokalemia, increased lactic acid, headache, and hyperglycemia. Inhaled route, in general, causes few systemic adverse effects. Patients with preexisting cardiovascular disease, especially the elderly, may have adverse cardiovascular reactions with inhaled therapy.	Drugs of choice for acute bronchospasm. Inhaled route has faster onset, fewer adverse effects, and is more effective than systemic routes. Oral systemic $beta_2$-agonists are not recommended. For patients who have intermittent asthma, regularly scheduled daily use neither harms nor benefits asthma control. Regularly scheduled daily use is not recommended. Regular use >2 d/wk for symptoms control (not EIB prevention), increasing use, or lack of expected effect indicates inadequate control For patients frequently using SABA, anti-inflammatory medication should be initiated or intensified. Levalbuterol at one-half the mcg dose produces clinically comparable bronchodilation and systemic side effects as racemic albuterol.

(Adapted from National Heart, Blood, and Lung Institute Expert Panel Report 3 (EPR 3): Guidelines for the Diagnosis and Management of Asthma. NIH Publication no. 08-4051, 2007.)

II. CONSIDERATIONS IN DELIVERY OF ASTHMA MEDICATIONS

A. Route and delivery. Medications for asthma can be administered by either local (inhaled) or systemic (ingested or parenteral) routes. The major advantage to inhaled therapy is delivering higher concentrations of drug directly to the airways while minimizing systemic side effects. When compared to systemic administration, local/aerosol delivery provides a more rapid onset of action with fewer side effects. When used properly, the traditional metered dose inhaler (MDI), dry powder inhalers (DPI), and nebulized forms provide comparable effects. However, the current Expert Panel Report (EPR-3) recommends the use of nebulized forms of bronchodilators for acute asthma in the emergency room.

B. Spacers and valved holding chambers (VHCs). The principal function of both spacers and VHCs is to retain large particles emitted from the MDI so that they do not deposit in the

oropharynx, thereby allowing a higher proportion of small, respirable particles to be inhaled. There is a large variability between devices regarding delivery of the respirable dose. Generally, VHCs are preferred over spacers as they both aggregate larger particles in the perimeter of the tube and allow patients a brief period in which to coordinate their inhalation. Currently, no specific combination of MDI and VHC has been specifically approved for use by the FDA.

III. SPECIFIC MEDICATIONS

A. Beta-2 adrenergic receptor agonists

1. Inhaled short-acting beta-2 adrenergic agonists (SABAs). The SABAs are the most important class of quick relief medications for asthma. Agonist-mediated stimulation of β_2 adrenergic receptors activates adeny-lyl cyclase, causing formation of intracellular cyclic-AMP with resultant bronchial smooth muscle relaxation. Significant effects of β-adrenergic stimulation in asthma include bronchodilation, facilitation of muco-ciliary clearance, and inhibition of mast cell mediator release, although whether β-agonists produce significant inhibition of mast cell mediator release *in vivo* is questionable. Several selective β_2-agonists are available including pirbuterol, albuterol, and levalbuterol (purified R-isomer of albuterol). In general, these agents are safe with few toxic effects even when used in high doses. However, some dose-dependent side effects are seen with β_2-selective agents, particularly when they are used orally, including tremor and tachycardia. Regarding possible differences between levalbuterol and albuterol, large clinical trials do not support any advantages of levalbuterol over albuterol.

While several earlier epidemiological studies suggested that the chronic, regular use of inhaled β_2-agonists might result in deterioration of asthma control and even an increased risk of death, more recent published studies in mild disease (on no additional medication) concluded that there was no difference in asthma control when albuterol was used on a regular basis compared to the use of albuterol as needed. Currently, it is recommended that albuterol and other SABAs be used on an as-needed basis only.

2. Inhaled long-acting beta$_2$-agonists (LABAs)

a. Clinical use. LABAs provide a longer duration of bronchodilation (~12 hours) when compared to the SABAs. The two inhaled LABAs currently available for the treatment of asthma include salmeterol and formoterol. Their properties are slightly different in that salmeterol is a partial beta-agonist and formoterol is a full beta-agonist. With regard to clinical properties, salmeterol has a slower onset of action (30 to 60 minutes) compared to formoterol. Neither LABA is recommended for treatment of acute symptoms or exacerbations. Both agents are highly beta$_2$ selective and therefore have dose-dependent sympathomimetic effects such as tremor. Additionally, there are clinically relevant cardiovascular side effects at doses four to five times higher than the recommended doses. These agents should not be used as monotherapy in the long-term control of asthma. Long-acting β-agonists should be used as adjuncts

to inhaled corticosteroids (ICS) to further control symptoms in patients with moderate and severe persistent asthma. They are also particularly useful for the control of nocturnal symptoms and the prevention of exercise-induced bron-chospasm (EIB). Several studies show that the LABA provides a more prolonged attenuation of EIB when compared to the short-acting beta-agonists. However, some studies suggest that the bronchoprotec-tive effect provided by LABA wanes with time. In spite of this, there seems to be no significant loss of bronchodilator efficacy with chronic LABA use. Long-acting beta-agonists also clearly decrease typical asthma exacerbations when they are added to an ICS.

Clinical studies have demonstrated an increased risk of severe asthma exacerbations, both life threatening and fatal, associated with regular LABA use when used as sole therapy for asthma. While all inhaled medications containing either salmeterol or formoterol currently carry "Boxed Warnings" regarding the elicitation of severe asthma, subsequent large meta-analyses have shown that there is no increased risk of severe attacks or death when LABAs are administered with concomitant inhaled corticosteroid (Table 9-3). Rather, these compiled data indicate that exacerbations of asthma are likely reduced by combining an inhaled corticosteroid plus LABA compared with patients taking an inhaled corticosteroid alone.

Table 9-3 Clinically Comparable Doses of Inhaled Corticosteroids

Drug	Comparative Daily Doses (μg)					
	Low		Medium		High	
	Child	Adult	Child	Adult	Child	Adult
Beclomethasone HFA	80–160	80–240	>160–320	>240–480	>320	>480
Budesonide DPI	180–400	200–600	>400–800	>600–1,200	>800	>1,200
Budesonide nebules	500	Unknown	1,000	Unknown	2,000	unknown
Ciclesonide	80–160	160–320	>160–320	>320–640	>320	>640
Flunisolide HFA	160	320	320	>320–640	≥640	>640
Fluticasone HFA	88–176	88–264	>176–352	264–440	>352	>440
Fluticasone DPI	100–200	100–300	>200–400	300–500	>400	>500
Mometasone DPI	110	220	220–440	440	>440	>440
Triamcinolone	300–600	300–750	>600–900	>750–1,500	>900	>1,500

(Adapted from Kelly WH. Comparison of inhaled corticosteroids: An update. *Ann Pharmacother* 2009;43:519–527.)

B. Corticosteroids

1. **Mechanisms of action.** Corticosteroids have broad anti-inflammatory effects and represent the single most important class of controller medication presently used to treat asthma. Potential mechanisms of action of corticosteroids include the modulation of nuclear regulatory proteins, catecholamine receptors, eicosanoid synthesis and function, vascular endo-thelial integrity, and transcription of proinflammatory cytokines (e.g., interleukins-1, 3, 4, 6, and 8). Other important functions include an increase in lipocortin-

1, which inhibits the production of lipid mediators of inflammation (e.g., leukotrienes [LTs] and prostaglandins), and inhibition of mucus secretion in airways. Chronic dosing with inhaled corticosteroids reduces the numbers of tissue eosinophils, lymphocytes, and basophils.

2. Inhaled corticosteroids (ICSs)

a. Clinical effects and dose responses. The regular use of ICS leads to significant reductions in the symptoms of chronic asthma, the use of rescue β_2-agonists, systemic corticosteroid use, number of asthma exacerbations, urgent care visits, hospitalizations, and deaths due to asthma. Physiologically, regular ICS usage results in improvements in pulmonary function (FEV_1 and domiciliary peak expiratory flow rates) and modest improvements in nonspecific bronchial hyperresponsive-ness. ICSs are a first-line agent for all forms of persistent asthma.

The comparative doses of ICS have been established through comparative clinical trials and are shown in Table 9-3. While this is a good general guide to steroid potency, other factors, particularly the steroid formulation and the delivery system used, have important effects on the amount of drug delivered to the patient and its potential for beneficial versus adverse effects. Most of the benefits of treatment are achieved with low-dose ICS although there is a dose response to ICS, which may vary depending on the response measured (i.e., lung function, exacerbation prevention, improvement in bronchial hyperre-sponsiveness, etc.). Studies have demonstrated that patients with mild to moderate asthma may gain only modest benefit from increasing doses of ICS, whereas patients with severe asthma benefit from high-dose therapy. However, control is achieved in a larger proportion of patients, and at a lower ICS dose, when used in combination with a LABA (see below).

b. Safety. Factors that determine both local and systemic effects include the total dose of ICS, the dosing schedule, whether or not a spacer device is used, and whether mouth rinsing is used.

i. Topical adverse effects. These include cough, oral candidiasis, and dysphonia. These can usually be avoided, minimized, or treated by using a spacer and good oral hygiene.

ii. Ocular effects. The relative risks for developing cataracts and ocular hypertension secondary to ICS appear to be very small. Asthmatics taking high doses of ICS for prolonged periods of time should be told of the possibility of developing ocular side effects and undergo regular eye examinations, especially in the setting of a family history of glaucoma. With regard to pediatric patients, low- and medium-dose ICSs appear to have no effect on the incidence of subcapsular cataracts or glaucoma.

iii. HPA axis effects. Clinically evident HPA axis suppression is unusual with ICS treatment, even at high doses. However, chemical HPA axis suppression, assessed by cosyntropin testing or 24-hour serum or urinary cortisol production, is frequently present in patients receiving high-dose ICS therapy. Any asthmatic taking large doses of ICS for long periods of time should be monitored for signs of adrenal insufficiency during acute physiologic stresses (e.g., surgery); supplementation with

systemic corticosteroids should be considered during these events.

iv. Bone density. Risks of reduced bone mineral density caused by ICS vary considerably across studies. One recent clinical trial in patients older than 65 years of age showed no increased risk of fractures at doses <2,000 μg/d of beclomethasone or equivalent. In patients at risk for osteoporosis or low BMD scores (e.g., prolonged inactivity, hypothyroidism), the use of bone-protecting therapies such as bisphosphonates may be considered. Efforts to minimize the dose of ICS with adjunctive therapy such as LABAs or LT modifiers should be employed when high doses of ICS are required to achieve satisfactory asthma control. Of note, low- and medium-dose ICSs appear to have no serious adverse effects on bone mineral density in children.

v. Growth effects. The measurable effects of corticosteroids on skeletal growth and development in children have also been variable. In the largest study performed to date, inhaled budesonide, 400 μg/d given for 4 to 6 years, has been demonstrated to cause a small but statistically significant reduction in growth velocity during the first year of treatment; this difference persisted at follow-up nearly 5 years later and was more pronounced in girls than in boys. There was no increase in the rate of fractures or reduction of sexual maturation during treatment or follow-up. While these data are important, it is equally critical to note that untreated or uncontrolled asthma in children also impacts significantly on growth velocity, which must be weighed against the small effects of growth with some ICS compounds.

C. Combination of ICS plus other therapies

1. **ICS plus LABA.** The addition of a LABA to an ICS results in greater improvements in FEV_1 and asthma symptom scores than use of higher doses of ICS alone. Although adding LTRA or theophylline to ICS has also been shown to improve outcomes, the weight of available evidence supports adding LABA to ICS.
2. **ICS plus leukotriene receptor antagonist (LTRA).** LTRAs have also been examined in combination with ICS. Both zafirlukast and montelukast have been shown to significantly improve pulmonary function and reduce exacerbation rates when used in combination with ICS. However, attempts to discontinue ICS in patients being treated with both ICS and LTRA have demonstrated that asthma symptoms and pulmonary function worsen, indicating that LTRA will not take the place of ICS in most patients.
3. **ICS plus theophylline.** Theophylline combined with low-dose budesonide has been shown to provide similar benefits when compared to high-dose budesonide used alone. While theophylline may confer a corticosteroid-sparing effect when used with low-dose ICS, it seems to provide less if any added benefit in contrast to LABA and the CysLT antagonists.
4. **Combination therapy in children.** Adjunctive therapy has not been adequately studied in patients 5 to 11 years of age and not evaluated at all in children under 4 years.

D. Leukotriene modifiers

1. **Role of LTs in asthma.** LTs are synthesized via the 5-lipoxygenation of arachidonic acid. This pathway has a branch point, which leads to the synthesis of either LT B_4 or the cysteinyl leukotrienes C_4, D_4, and E_4. L T B_4 is a potent chemoattractant for granulocytes.

The cysteinyl leu-kotrienes exert their effects by binding to the $CysLT_1$ or $CysLT_2$ receptors; most of the actions of cysteinyl leukotrienes important in asthma are mediated by the $CysLT_1$ receptor. These actions include the contraction of human airway smooth muscle, stimulation of mucus secretion, and increase in vascular permeability.

2. **Leukotriene inhibitors.** Abrogating the effects of the cysteinyl leukot-rienes can be accomplished either by inhibiting the 5-lipoxygenase with a 5-lipoxygenase inhibitor (zileuton) or by blocking the $CysLT_1$ receptor (montelukast, zafirlukast).

a. Leukotriene receptor antagonists (LTRAs)

i. **Clinical use.** Antagonists for the CysLT1 receptor include mon-telukast and zafirlukast, which are administered as oral preparations. Both of these medications are indicated for the treatment of persistent asthma; montelukast is approved down to age 1 year and zafirlukast to age 7 years. LTRAs lead to improvements in lung function 1 to 3 hours after the first dose. The bronchodilator effect is greater in patients with more airway obstruction, and the magnitude of this effect is about half that of the response to β_2-agonists. The bronchodilator effects of LT modifiers and LABAs are partially additive, suggesting that administration of both may be indicated for some patients. These drugs also decrease the need for rescue treatment with SABAs, relieve asthma symptoms, decrease the frequency of exacerbations requiring oral glucocorticoid therapy, and decrease the dose of ICS required to maintain control of asthma. With regard to Expert Panel guidelines, LTRAs are considered alternative therapy for mild persistent asthma. They can be used as adjunctive therapy with ICSs but are not preferred compared to the addition of LABAs (in youths >12 years and adults). Montelukast is also indicated for exercise-induced asthma, and this effect does not diminish after chronic use, unlike that observed with the regular use of a LABA. Since exercise stimulates bronchoconstriction in 70% to 80% of patients with asthma, these agents might be especially useful in asthmatics in which exercise is an important trigger.

ii. **Safety of LTRAs.** Cases of severe hepatic dysfunction have occurred with zafirlukast. A syndrome similar to the Churg-Strauss syndrome with marked circulating eosinophilia, cardiac failure, and associated eosinophilic vasculitis has been reported in a few patients treated with zafirlukast or montelukast in several case studies. This syndrome is rare and has been thought to represent the clinical unmasking of preexisting and previously undiagnosed Churg-Strauss syndrome. Drug–drug interactions have also been reported, and zafirlukast can cause an increase in the levels of warfarin.

b. 5-Lipoxygenase (5-LO) inhibitors

i. **Clinical use.** Zileuton is the only available 5-LO inhibitor approved for the treatment of chronic asthma in patients older than 12 years of age. Similar to the LTRAs, it has been shown to increase FEV_1 in patients with mild to severe asthma, improve asthma symptoms, and decrease beta-agonist use. It has been shown to be particularly useful in patients with aspirin-exacerbated respiratory disease and may have beneficial effects upon upper airway symptoms in patients with chronic

sinusitis and nasal polyposis. Currently, the Expert Panel notes that zileuton can be used as alternative adjunc-tive therapy in adults.

ii. **Safety**. Zileuton can cause elevations in serum aminotransferases. Most laboratory abnormalities occur during the first 3 months of therapy and often resolve spontaneously or with the discontinuation of therapy. Rare cases of liver failure have been reported. Zileuton can cause an increase in the half-life of warfarin and is a microsomal cytochrome P450 inhibitor that can inhibit the metabolism of the-ophylline. Thus, doses of both warfarin and theophylline should be monitored closely when used in combination with zileuton.

E. Methylxanthines

1. **Clinical use.** Methylxanthines inhibit the enzyme phosphodies-terase, which leads to an increase in intracellular cAMP in airway smooth muscle and causes bronchodilation. These agents may also improve diaphragmatic function as well, which is more relevant to COPD than asthma. The most frequently used methylxanthines are theophylline and aminophylline. Aminophylline has been available for many years for parenteral use and is typically used to treat status asthmaticus. Data suggest that parenteral aminophylline adds little to the management of status asthmaticus if high-dose inhaled SABAs are already in use. Theophylline is less effective than low-dose ICS used alone, and the addition of theophylline to ICS results in modest improvement in lung function similar to doubling the dose of ICS. Thus, theophylline may be used as nonpreferred adjunctive therapy to ICS.
2. **Safety.** The methylxanthines have a narrow therapeutic index, and close monitoring of serum levels is required. A serum concentration of between 5 and 12 μg/mL is typically recommended for chronic the-ophylline therapy. Close monitoring of serum concentrations is necessary in patients with liver disease, congestive heart failure, pregnancy, and when certain drugs such as macrolide and quinolone antibiotics and cimetidine are being used. If close monitoring is impossible, the daily dose should not exceed 10 mg/kg/d in adults. Signs and symptoms of theophylline toxicity include nausea, vomiting, palpitations, and tremor. Malignant arrhythmias, seizures, and even death have been reported, particularly with high serum levels.

F. Anticholinergic agents

Parasympathetic nerves are the dominant bronchoconstrictor neural pathways in human airways. Cholinergic pathways via the vagus nerve contribute to the diurnal variation in airway tone seen in most asthmatics. Anticholinergic agents are less potent bronchodilators than $beta_2$-agonists for asthma, and their efficacy in the long-term management of asthma has not been demonstrated. Ipratropium is a quaternary ammonium derivative of atropine sulfate without the side effects of atropine and has been shown to provide additive benefit when used with inhaled $beta_2$-agonists for acute asthma and status asthmaticus and may reduce hospital admission rates as well. Tiotropium bromide is a newer anticholinergic agent with longer duration of action and is approved for the treatment of COPD. While it does not yet have an indication in treating chronic asthma, emerging data suggest that it may be an effective adjunct to ICS when LABAs are contra-indicated or found to be ineffective.

G. Omalizumab

1. **Role of IgE in asthma.** IgE plays an important early role in the development of allergic asthma through initiation of the mast cell inflammatory cascade. The key role of IgE in asthma pathogenesis is supported by epi-demiological studies showing that serum IgE levels correlate closely with cutaneous reactivity to common allergens and the prevalence of asthma and bronchial hyperresponsiveness. Because IgE plays a role early in the sequence leading to early and late responses to allergens, bronchial hyperreactivity, and possibly airway remodeling, it is a very attractive and specific target for asthma therapy.
2. **Omalizumab mechanism of action.** Omalizumab is a humanized monoclonal antibody directed against the F_c epsilon RI binding site on IgE. It is composed of both human (95%) and murine (5%) elements and is nonimmunogenic. When omalizumab binds to free IgE, it forms an immune complex that cannot interact with the FcεRI receptor on effector cells. As IgE is inhibited from binding to mast cells and baso-phils, these cells can no longer be activated by allergen. Omalizumab has also been shown to reduce FcεRI receptor numbers on circulating baso-phils as well as a number of tissue-bound cells. Omalizumab has also been shown to decrease numbers of sputum and bronchial eosinophils and $CD3^+$, $CD4^+$, and $CD8^+$ T cells in bronchial biopsy.
3. **Clinical use.** Omalizumab is currently approved for use in moderate to severe asthma uncontrolled by ICS in patients older than 12 years of age with total IgE between 30 and 700 IU/mL and IgE-mediated hypersen-sitivity to a perennial allergen, such as house dust mite, animal dander, cockroach, or mold. The drug is administered by subcutaneous injection every 2 to 4 weeks based upon patient weight and total IgE. While serum concentrations peak between 3 and 14 days after subcutaneous administration, it may take as long as 4 months to see maximum clinical benefits with the drug. Addition of omalizumab to ICS has been shown to significantly reduce asthma exacerbations, decrease the amount of ICS required to maintain control of asthma, improve asthma symptoms and asthma-related quality of life, cause small but significant improvements in lung function, and reduce both emergency room utilization and hospitalization for asthma. Omalizumab has also been shown to decrease the rate of exacerbations in patients receiving ICS plus LABA therapy. Once omalizumab has been started, performance of free serum IgE levels, *in vitro* tests of specific IgE, and allergy skin tests may no longer be accurate or valid.
4. **Safety.** Severe systemic allergic reactions have been reported as adverse events associated with omalizumab. Most reactions occur within 2 hours of dosing and are most common after the first three injections. However, a significant portion of the reactions have been reported after receiving many doses and may occur several hours after administration. Therefore, it is important that omalizumab is administered by physicians trained in and prepared for the management of anaphylaxis. Other adverse effects reported in trial data include injection site pain and bruising. While malignant neoplasms were observed in a small number of omalizumab-treated patients (0.5%) compared to control patients after the completion of phase 3 clinical trials, a careful analysis of all data has revealed no causative association between omalizumab and cancer.

H. Macrolide antibiotics

Macrolides such as troleandomycin and erythromycin have been shown to be effective in the treatment of asthma. Their mechanism of action is mediated, in part, by reduced corticosteroid

metabolism. Additionally, erythromycin and the newer macrolides (e.g., azithromcyin, clarithromy-cin, roxithromycin) demonstrate anti-inflammatory effects, including antioxidant effects and inhibition of cytokine secretion. Along with this effect, many severe asthmatics have been shown to harbor atypical organisms (i.e., *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*) chronically in the lower airways, which may act as a long-term trigger of asthma and potentially improve with administration of macrolide antibiotics. Clinical data have been mixed, but a beneficial effect on BHR seems to be a consistent finding. Given the available data, a several week trial of a macrolide may be useful in patients with asthma dependent upon chronic treatment with oral corticosteroids or in patients in whom the above microorganisms are identified by sputum analysis or bronchoscopic sampling. It is important to remember that the use of macrolide therapy does carry a risk of hepatic toxicity.

IV. OTHER FORMS OF ASTHMA TREATMENT

A. Allergy immunotherapy

Immunotherapy has been used extensively as a treatment for allergic asthma, and a large number of clinical studies demonstrate significant improvement in both children and adults. These benefits include decreases in asthma symptoms and SABA use, increases in pulmonary function, and reductions in both nonspecific and allergen-specific bronchial responsiveness. As a general rule, allergy immunotherapy should not be administered to patients with moderate to severe asthma, and the FEV_1 should be above 70% of predicted prior to immunotherapy injections. Data from pediatric studies suggest that immunotherapy may be a more effective form of treatment for asthma when administered early in the course of the disease and may even prevent the development of asthma when administered to patients with allergic rhinitis. This topic is fully reviewed in the chapter on Immunotherapy for Airway Disease.

B. Bronchial thermoplasty

Bronchial thermoplasty is a relatively new treatment, which has been approved by the FDA for patients older than 18 years of age with severe asthma that is poorly controlled despite the use of ICS and LABA therapy. Generally done in three outpatient visits, bronchial thermoplasty heats the insides of the airways in the lungs with an electrode. This treatment reduces the amount of smooth muscle inside the airways, thereby limiting the ability of the airways to constrict. Bronchial thermoplasty has been demonstrated to reduce severe exacerbations of asthma (including those leading to emergency room visits) and time lost from work and school due to asthma. In addition, this procedure has been shown to improve asthma-specific quality of life. Bronchial thermoplasty is routinely performed under moderate sedation or light anesthesia. Bronchial thermoplasty is not widely available at the present time, and more long-term research is needed to determine whether the benefits of this treatment are cost-effective and significantly outweigh the possible risks.

V. MANAGEMENT OF ASTHMA EXACERBATION IN THE OUTPATIENT SETTING

A. Assessment of acute exacerbations

Patients should be instructed to recognize the symptoms of an asthma exacerbation in its early stages. Data suggest that exacerbations caught early and treated within 6 hours of onset can reduce the need for hospitalization. Clinical warning signs include but are not limited to exertional dyspnea, nocturnal awakenings and coughing, and increased rescue MDI usage. Patients should learn to recognize factors that may lead to an exacerbation like an oncoming allergic season or viral upper respiratory infections. Some experts advocate the monitoring of PEFR on a daily basis for all asthmatics but especially those with frequent exacerbations. Some data suggest that the PEFR will begin to fall prior to the development of overt symptoms. The obvious advantage is that the early detection of an exacerbation can lead to a "step-up" in anti-inflammatory therapy, thus aborting an exacerbation before it requires acute care. Of note, PEFR may be especially beneficial in those patients who poorly perceive their asthma symptoms.

In determining the management of an acute exacerbation, the health care professional should first ascertain the severity of an asthma exacerbation. Patients should be questioned about the presence of symptoms like cough, breathlessness, wheeze, and chest tightness. Knowing whether nocturnal symptoms are present, whether there has been a significant decrease in PEFR, and the amount of recent rescue MDI use can help to establish the severity of an exacerbation. Additionally, prior to deciding whether to treat asthma in the home setting, one needs to decide if the patient has adequate social support and the ability to seek medical attention in case there is deterioration in the face of intensified therapy.

B. Initial treatment

One may begin treatment with an inhaled SABA, dosing up to three times in the first hour. If the response to SABA is satisfactory (i.e., relief of symptoms within 4 hours), the SABA should be continued every 3 to 4 hours for 1 to 2 days and then taken as-needed afterward. If the response to SABA is partial (i.e., initially good response but recurrence of symptoms within 3 hours and peak flow rate between 50% and 79% of predicted or personal best), add a course of corticosteroids (adults: prednisone 40 to 80 mg/d for 5 to 7 days, children: 1 to 2 mg/kg/d with a maximum of 60 mg/d), continue SABA, and follow up within 12 to 24 hours. If the response to SABA is unsatisfactory (i.e., persistent or deteriorating symptoms despite SABA and/or PEF <50% of predicted or personal best), start oral corti-costeroids, continue frequent doses of SABA, and recommend a prompt visit to the ED. It is generally accepted practice that patients start taking oral corticosteroids only after the clinician has been contacted, unless there is a standing action plan that outlines their addition. With regard to ICS, some data suggest that quadrupling the dose of ICS for 7 days is effective in preventing full-blown exacerbations; this approach may be worth trying in patients who tolerate oral corticosteroids poorly.

VI. SPECIAL CONSIDERATIONS IN ASTHMA THERAPY

A. Aspirin-exacerbated respiratory disease

1. **Diagnosis.** It is estimated that 20% of adults and 5% of children with asthma have aspirin-induced asthma, formerly called Samter's triad and more recently referred to as aspirin-exacerbated respiratory disease (AERD). Patients with AERD develop wheezing and

other chest symptoms with or without facial flushing and nasal congestion and rhinorrhea after taking aspirin as well as other nonsteroidal anti-inflammatory (NSAID) medications. In general, patients with AERD have concomitant chronic sinusitis with nasal polyposis, and their asthma is often severe and more difficult to treat than asthmatics without nonsteroidal sensitivity. AERD most often develops after the third decade of life

For the most part, diagnosis of AERD is based upon a clinical history of severe reactions following NSAID ingestion. In patients with severe asthma and chronic sinusitis with nasal polyposis who have not had the occasion to use a NSAID for a long period of time, it is judicious to empirically avoid the use of NSAIDs. However, if it is uncertain whether a patient has NSAID sensitivity and they require the use of low-dose aspirin for cardiovascular disease prophylaxis or an NSAID for treatment of pain, an incremental oral challenge should be performed with the NSAID of choice (See appendix in chapter on Drug Allergy). In general, because of the risk of severe respiratory reactions, NSAID challenges should be performed in a highly monitored area with provisions for treating acute severe asthma.

2. **Treatment.** Patients with AERD should be treated with usual asthma medications appropriate to control their symptoms and maintain their pulmonary function, including ICS and LABA. In addition, LT modifiers, including LTRA and 5-LO inhibitors, may be particularly useful in patients with AERD. Both classes of drugs have been shown to blunt the development of symptoms following aspirin challenge. Similarly, both classes of medications improve pulmonary function and reduce beta-agonist use when used by aspirin-sensitive asthmatics. Because of the demonstrable benefit, the LT-modifying drugs should be considered as first-line therapy in the asthmatic patients with AERD.

Desensitization with aspirin (or other NSAID) should be employed in patients who have strong histories of aspirin reactions and require aspirin or other NSAID, as described above. Aspirin desensitization can also be employed as a therapeutic modality in patients with AERD to reduce the severity of their chronic sinusitis and asthma. Aspirin desen-sitization has been shown to significantly reduce nasal and sinus symptoms, asthma symptoms, the dose of chronic oral corticosteroids, and the need for sinus surgery in patients with AERD. Once desensitization is achieved, cessation of aspirin therapy leads to the loss of desensitization in most cases in 24 hours or less. Because of this, patients must be counseled regarding the potential serious risks of stopping and starting aspirin and the need for absolute compliance once this regimen has been initiated. Many patients do discontinue treatment after several weeks to months because of gastrointestinal side effects such as dyspepsia and/or gastric bleeding. A protocol for aspirin desensitization is presented in the Appendix in the chapter on Drug Allergy.

B. Management of the pregnant asthmatic

Asthma is the most common respiratory disease in women of reproductive age. Pregnancy represents a unique physiological state that has significant effects on asthma. Roughly one third of patients will experience a worsening of their asthma with pregnancy, one third will improve, and one third will not experience a change. Fortunately, labor and delivery do not worsen asthma in most patients. Prepregnancy asthma severity and measurements of pulmonary function are not useful predictors of clinical deterioration. Asthma is generally less severe during the last month of pregnancy; however, those who worsen typically will worsen during the third trimester. One of the reasons for asthma deterioration may be the cessation of

controller medications by expectant mothers after they realize they are pregnant. In addition to asthma worsening, there also seems to be a small increase in pregnancy-related complications in asthma patients. In spite of these concerns, asthma should not be considered a contraindication to pregnancy because the risks can be significantly modified with proper monitoring and therapy.

The goals of therapy in the pregnant patient are similar to those of any asthmatic. The proper use of controller medications should maximize lung function and activity while minimizing symptoms and preventing exacerbations. Objective monitoring of lung function is of particular importance in pregnancy since worsening respiratory symptoms may be due to asthma, other cardiopulmonary disease(s), or dyspnea associated with pregnancy; properly performed spirometry should be able to differentiate between these possibilities. The pathogenesis of the dyspnea of pregnancy is poorly understood, but progesterone-mediated hyperventilation is probably at least partially responsible. Dyspnea related to pregnancy is not caused by airflow obstruction, and FVC, FEV_1, and FEV_1/FVC ratio all remain normal.

With regard to medical therapy, efficacy for both controller and rescue therapy is largely extrapolated from studies involving patients who were not pregnant. Although data on adverse effects in pregnancy are largely observational, most findings are reassuring. Asthma drugs with large experiences during pregnancy include both albuterol and budesonide.

C. Treating asthma in children and the elderly

1. **Asthma treatment in children.** Asthma is of particular concern in children given its prevalence and difficulty in objectively assessing control. It is estimated that 50% to 80% of children who have asthma develop the disease by their fifth birthday. Asthma in childhood is frequently underdiagnosed, and therefore, many children do not receive adequate therapy. Diagnosis of asthma in children younger than 5 to 6 years of age is based upon history and physical findings, as patients of this age are usually incapable of performing adequate spirometry. As with adults, a stepwise approach to therapy should be undertaken with dosage and frequency of medications increased as necessary and decreased when possible. Treatment of asthma in young children, especially younger than 4 years of age, should be in the form of a therapeutic trial. If no response is seen in 4 to 6 weeks, then therapy should be discontinued and alternative diagnoses considered. Therapy should then be stepped down if there is a clear and positive response after a 3-month period. When considering step-up therapy, consideration should be given to the age of the child. For children <4 years of age who are not well controlled on low-dose ICS, increasing the dose of ICS to medium dose is recommended prior to adding adjunctive therapy. With regard to children older than 4 years, increasing the dose to medium dose and adding adjunctive therapy to a low dose of ICS are considered to be equivalent. Overall, the choice of therapy should include the history of responsiveness to prior therapies and the ability of the patient and family to properly use the medication. School-age children should have a written asthma action plan for asthma exacerbations during school or childcare; studies have demonstrated the usefulness of written action plans in schools.
2. **Asthma treatment in the elderly.** Whereas the onset of asthma more commonly occurs during the first two decades of life, asthma may also begin later in life. Available

evidence suggests that patients developing asthma in mid-life to old age underreport symptoms and present later in their disease progression compared to younger patients. Older patients also demonstrate lower awareness of bronchoconstriction and frequently underrate their asthma symptoms; both problems may be further potentiated by cognitive decline associated with aging.

The main methods of asthma management remain the same across age groups. Unfortunately, adherence to asthma treatment regimens has been shown to decline with age. Factors shown to affect adherence include economic considerations, concerns regarding side effects, and perceived efficacy.

D. Scuba diving in the patient with asthma

When a scuba diver descends below the surface of the ocean, the lungs are exposed to hyperbaric conditions. Rapid uncontrolled ascent during a scuba dive can result in the dissection of gas along the perivascular sheaths and into the pleural space (pneumothorax) or pericardium (pneumopericardium). Similarly, gas can enter the pulmonary veins and cause a gas embolism. Gas embolism is the second most common cause of accidental death during recreational diving. In theory, the asthmatic may have areas of the lung that empty slowly because of airway obstruction. Such areas may be predisposed to air trapping and subsequent barotrauma during ascent. Some retrospective data suggest that small-airway obstruction might increase the incidence of barotrauma in divers with asthma. Obstruction in the small airways can be assessed using maximal midexpiratory flow rates ($FEF_{25\%}$, $FEF_{25\%–75\%}$). Inhalation of cold, dry air during a scuba dive could aggravate bronchospasm in the asthmatic, adding further to the risks of barotraumas noted above.

Unfortunately, there are no population studies of any significant size that examine the risk of either barotrauma or mortality in divers with asthma. Because of the lack of good data to give accurate risk estimates and the fact that many thousands of patients with asthma dive without untoward effects, a pragmatic approach should be used. First, asthma must be well controlled in any patient considering diving. Second, the diver should be knowledgeable enough to both recognize the warning signs of worsening asthma and to avoid diving when asthma is not well controlled. Third, because diving is an inherently dangerous sport, the diver should participate in the decision to dive, just as any patient would consider any procedure with inherent risk. In other words, rather than providing medical clearance of a patient with asthma for diving, having the patient give informed consent encourages the patient to understand the risks associated with the activity and to take shared responsibility for the decision.

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10

Immunologic Diseases of the Lung

Shefalee Amin, Michelle R. Zeidler, Eric C. Kleerup

The lung is an important and vulnerable target in immunologic diseases. Not only does the lung participate in systemic immunopathologic processes, but it is also capable of initiating local immune responses that may be beneficial or adverse to the host. With the exception of asthma, primary and secondary immunologic lung diseases are discussed in this chapter according to their presentation, immunologic features, pathologic features, diagnostic criteria, differential diagnosis, treatment, and prognosis. These various entities are either known or proposed to have immunologic mechanisms and include hypersensitivity pneumonitis, allergic bronchopulmonary aspergillosis (ABPA), eosinophilic lung diseases, antiglomerular basement membrane syndrome, Wegener's granulomatosis, sarcoidosis, i diopathic pulmonary fibrosis (IPF), nonspecific interstitial pneumonia, and cryptogenic organizing pneumonia (COP) of the lung.

HYPERSENSITIVITY PNEUMONITIS

Hypersensitivity pneumonitis **(extrinsic allergic alveolitis)** is a common and well-studied immunologically mediated lung disease. It occurs after the inhalation of organic dusts and is an IgG-mediated response. The result is a diffuse pulmonary process consisting of reticulonodular or alveolar processes (or both) with poorly formed granulomas. In contrast to other granulomatous diseases (e.g., sarcoidosis, coccidioidomycosis), the immunopathologic process is localized in the lung, and there is no systemic involvement. Moreover, it can fully remit if the antigenic stimulus is removed. Hypersensitivity pneumonitis develops in only 5% to 15% of the exposed population, and the majority of patients are nonatopic and nonsmokers. The antigenic materials may be of animal, vegetable, fungal, bacterial, or chemical origin. Reactions can be classified as acute or chronic. In general, there is no age, sex, or significant geographic predilections other than those related to specific occupational exposures.

I. CLINICAL PRESENTATION

The antigens listed in Table 10-1 are recognized as capable of sensitizing susceptible persons and subsequently causing hypersensitivity pneumonitis. This is only a partial list, and new sources from occupational exposure, homes, and hobbies are reported annually. Despite this long expanding list, these inciting antigens have striking similarities in their clinical, radiographic, and pathologic outcomes.

A. Acute hypersensitivity pneumonitis occurs when exposure is heavy but intermittent.

Table 10-1 Principal Causes of Hypersensitivity Pneumonitis

Antigen Source	Exposure History	Disease
Thermophilic bacteria		
Faenirecti rectivirgula	Potatoes	Potato riddler's lung
Micropolyspora faeni, M. polyspora Thermoactinomyces candidus, T. vulgaris	Hay, straw	Farmer's lung
M. faeni	Grain	Grain handler's lung
T. sacchari. T. vulgaris	Pressed sugar cane	Bagassosis
T. vulgaris, T. candidus, M. faeni	Heated water reservoirs	Humidifier lung
Other bacteria		
Actinobifida dichotomica	Mushrooms	Mushroom worker's lung
Bacillus subtilis	Detergent manufacture	Detergent worker's lung
B. subtilis	Water reservoirs	Humidifier lung
True fungi		
Alternaria sp.	Various wood pulps	Woodworker's lung
Aspergillus fumigatus, Aspergillus clavatus	Barley	Malt worker's disease
Aspergillus sp.	Tobacco plants	Tobacco grower's lung
Botrytis cinera	Wine grapes	Winemaker's lung
Cryptostroma corticale	Maple bark	Maple bark stripper's lung
Mucor solonifer	Paprika pods	Paprika splitter's lung
Penicillium caseii	Aged cheese	Cheese washer's lung
Rhizopus sp., *Mucor* sp.	Maple bark	Wood trimmer's disease
Trichosporon cutaneum	House dust (Japan)	Summer type hypersensitivity
Animal proteins		
Bat droppings	Bat	Bat lung
Bird serum, excreta	Parakeets, pigeons, canaries, ducks	Bird breeder's lung
Feathers	Galliformes (poultry)	Poultry worker's lung
Fox fur	Fox	Furrier's lung
Sitophilus granarius	Grain (wheat weevil)	Miller's lung
Vegetable matter		
Coffee bean dust	Coffee beans	Coffee worker's lung
Cork	Cork dust	Suberosis
Cotton	Bract of cotton flower	Byssinosis
Tea plants	Tea	Tea grower's lung
Thuja plicata	Red cedar dust	Cedar worker's lung
Chemicals		
Bacillus subtilis enzymes	Washing powder	Detergent worker's lung
Copper sulfate	Vineyard antifungal	Vineyard sprayer's lung
Methylene diisocyanate, toluene diisocyanate	Polyurethane foam or rubber manufacture	Chemical worker's lung
Trimellitic anhydride	Plastics	Chemical worker's lung
Ventilation and water-related contamination		
Aureobasidium sp.	Sauna	Sauna taker's lung
Cladosporium sp., *Mycobacterium avium* complex	Hot tubs	Hot tub lung
T. vulgaris, T. sacchari, T. candidus	Humidifer	Humidifier feve

1. **Symptoms and signs.** Acute symptoms, including fever, chills, dyspnea, chest tightness and dry cough, appear 4 to 6 hours after each exposure and remit when the agent is avoided. This is considered a late, or Arthus (type III), immune reaction. Physical exam reveals fever, tachypnea, tachycardia, and a few lung rhonchi or crackles.
2. **Laboratory findings.** Laboratory tests are of limited utility. Peripheral neutrophilia (without eosinophilia) and increased IgG levels, including antigen-specific IgG, are common in the acute form. Serum IgE levels are usually within normal limits. Nonspecific markers of inflammation such as an elevated ESR, C-reactive protein, and rheumatoid factor may also be present.

3. **Radiographic findings.** Radiographic abnormalities will typically develop with repeated antigen exposure but may not parallel the severity of disease. Up to 4% of patients may have normal x-rays, while up to 45% may have very subtle changes. Initially, diffuse airspace opacification is present on x-rays. This resolves into a fine nodular or reticulo-nodular pattern. These changes may be completely reversible over 4 to 6 weeks if the initiating exposure is avoided. High-resolution computed tomography (HRCT) has a higher sensitivity and specificity for detecting lung involvement and may be useful in cases where routine chest x-rays show only subtle findings or are normal. Findings on HRCT include scattered, small, rounded opacities in a centrilobular distribution as well as patchy airspace opacification.
4. **Physiologic tests.** Pulmonary function tests show hypoxemia and a restrictive ventilatory defect, with reduced vital capacity, total lung capacity, diffusing capacity, and static compliance. Airway obstruction is not typical unless the patient is atopic or has a concurrent obstructive pulmonary disease. Nonspecific airway hyperreactivity can be seen.

B. Acute hypersensitivity pneumonitis in asthmatic patients. Approximately 10% of patients with hypersensitivity pneumonitis have atopy and asthma. A two-stage reaction develops in these patients if they are exposed to organic dust. The immediate asthmatic, or type I, immune reaction will be manifested by dyspnea, wheezing, and an obstructive ventilatory defect. This reaction subsides and is followed in 4 to 6 hours by a type III immune reaction.

C. Subacute or intermittent HP

1. **Symptoms and signs.** Subacute hypersensitivity pneumonitis is characterized by the gradual development of productive cough, dyspnea, fatigue, anorexia, and weight loss. Physical exam typically reveals tachy-pnea and diffuse rales.
2. **Laboratory findings.** The major laboratory abnormality is lymphocytosis in bronchiolar lavage fluid.
3. **Radiographic findings.** As in acute H P, chest radiography can appear normal or show micronodular or reticular opacities. Abnormalities on HRCT include diffuse micronodules, ground-glass attenuation, focal air trapping, and with more prolonged disease cicatricial emphysema or mild fibrotic changes. These findings also undergo dramatic improvement with treatment with glucocorticoids or with removal of the antigen.
4. **Physiologic testing.** Pulmonary function testing typically has a restrictive abnormality or a mixed obstructive and restrictive pattern. The diffusion capacity (DLCO) is also reduced in most cases.

D. Chronic hypersensitivity pneumonitis occurs when the exposure is mild but more continuous (e.g., from a single parakeet).

1. **Symptoms and signs.** Progressive dyspnea, decreased exercise tolerance, productive cough, and weight loss develop insidiously. Acute episodes of chills and fevers are less likely. Wheezing, bibasilar crackles, cyanosis, clubbing, and cor pulmonale develop as pulmonary inflammation and fibrosis progress.
2. **Radiographic findings.** The diffuse nodular and reticulonodular pattern characteristic of the acute and subacute stages is superimposed on fibrosis and honeycombing and loss of lung volume and compensatory over inflation (emphysema) of the less involved lung

zones. These changes are typical of diffuse interstitial fibrosis of any origin and indicate irreversible damage to the lungs. HRCT may be useful for distinguishing hypersensitivity pneumonitis from IPF, which usually exhibits more extensive honeycombing and a predominance of changes in the peripheral and lower lung zones.

3. **Physiologic testing.** Pulmonary function tests show severe restrictive disease, with variable airway obstruction and air trapping.

II. IMMUNOLOGIC FEATURES

A. Immunopathogenesis. HP is characterized both by proliferation of $CD8^+$ cytotoxic lymphocytes and by an exuberant production of antibody, especially IgG, to offending antigens.

1. **Acute phase: macrophage–lymphocyte response.** After inhalation of an offending antigen, it binds IgG forming an immune complex, which subsequently initiates a complement cascade resulting in activated macrophages. These macrophages secrete chemokines and cytokines that first attract neutrophils and, after several hours, attract T lymphocytes and monocytes. Increased numbers of $CD4^+$ TH1 cells appear in the BAL fluid shortly after exposure, but in most cases of H P, $C8^+$ cells predominate later. This results in a reversal of the usual $CD4^+$:$CD8^+$ ratio ($\leq$1:2) (normal 1.2–1.6:1), which is opposite of the alteration observed in sarcoidosis ($CD4^+$:$CD8^+$ratio $\geq$ 2:1). These $CD8^+$ cells are composed of both activated suppressor ($CD8^+$) and cytotoxic ($CD8^+$ and $CD56^+$) lymphocytes.
2. **Subacute phase: granuloma formation.** After recruitment into the lung and activation, the young macrophages develop into epithelioid cells and multinucleated giant cells. Lymphoid follicles containing plasma cells also develop in the lesions during the subacute phase.
3. **Chronic phase: fibrosis.** Early collagen formation by myofibroblasts occurs, and the extracellular matrix surrounding the granuloma becomes rich in the proteoglycan versican. Activated alveolar macrophages express increased amounts of TGF-ß, a potent stimulator of fibrosis and angiogenesis

B. Serum precipitins. The characteristic immunologic feature of hypersensitivity pneumonitis is the presence of precipitating (usually IgG) antibody to the offending antigen. Serum antibodies or precipitins are readily and reproducibly demonstrated by the Ouchterlony double immunodiffusion technique. However, the presence of serum precipitins reactive to an antigen present in the patient's environment is not prima facie evidence that it is the causal antigen in hypersensitivity pneumonitis. Although the **positive precipitin test** is clinically helpful, it actually indicates prior exposure and sensitization and does not necessarily correlate with clinical sequelae. Precipitins are observed in 90% of patients with active farmer's lung, but the percentage with detectable antibodies falls as time passes. Serum precipitins without clinical pneumonitis can develop in up to 50% of exposed asymptomatic patients. Conversely, there are rare patients with clinical disease and no demonstrable antibodies. Antibodies can be demonstrated by more sensitive techniques such as ELISA, immunoelectrophoresis, and immunofluorescence, although their specificity is lower. The correct antigen must be used to detect the antibodies, but many causative antigens have not been identified. Thus, a negative

precipitin test in the face of convincing clinical evidence does not exclude the diagnosis, whereas a positive test without appropriate clinical findings does not establish a diagnosis.

C. Skin testing. Antigens for thermophilic actinomycetes and many molds result in a nonspecific irritant response that interferes with skin testing. Cutaneous anergy may also develop from increased suppressor T-cell activity. Many antigens provide a high percentage of positive responses even in exposed but unaffected individuals. Skin testing is therefore neither specific nor sensitive in determining the cause or presence of hypersensitivity pneumonitis. Skin testing for immediate, late-onset or delayed reactions does **not** currently have a role in diagnosis or management of hypersensitivity pneumonitis.

III. PATHOLOGIC FEATURES

All forms of hypersensitivity pneumonitis have similar and nonspecific pathologic features regardless of the inciting agent. The histologic reflection of precipitating antigen–antibody complexes and activation of the complement cascade in lung tissue are best demonstrated in early hypersensitivity pneumonitis as the fibrosis seen in the chronic phase is nonspecific. The histology of hypersensitivity pneumonitis includes (1) a mononuclear interstitial infiltration with a bronchocentric distribution (100%); (2) poorly formed noncaseating granulomas surrounding bronchioles (70%); and (3) airway inflammation with foamy macrophages (65%), often associated with bronchiolitis obliterans (50%). Over the course of several months, the histology becomes nonspecific as the granulomas disappear and interstitial fibrosis and obliterative bronchiolitis predominate, resulting eventually in honeycomb cysts and end-stage fibrosis.

IV. DIAGNOSTIC APPROACH

HP can be an elusive diagnosis and challenge even the experienced clinician. As HP can mimic multiple diseases, the diagnosis is founded on a high index of suspicion coupled with suggestive radiographic, physiologic, and immunologic findings.

A. A high index of suspicion is based on a detailed environmental history. Although patients often associate recurrent exposures with symptoms in the acute form of hypersensitivity pneumonitis, the exposure in the chronic form is much more difficult to identify.

B. Chest x-rays, HRCT, and pulmonary function tests consistent with hypersensitivity pneumonitis.

C. Serum precipitins and BAL consistent with hypersensitivity pneumonitis. As stated above, negative studies do not rule out disease, while positive studies do not necessarily confirm a diagnosis. BAL may be done as an adjunct to rule out infection but is not a routine test required for the diagnosis of hypersensitivity pneumonitis.

D. Histologic findings consistent with hypersensitivity pneumonitis. This can usually be done with good transbronchial biopsies directed by radiographic findings, although occasionally (usually in the chronic form) an open lung biopsy is preferred. Special stains and cultures to rule out infectious etiologies should be sent.

E. Trial of avoidance and/or controlled reexposure to the suspected antigen or environment. Deliberate repetition of natural exposure to the suspected antigenic environmental source (e.g., barn, factory) and observing the clinical response (by physical examinations, chest x-rays,

and/or spirometry before and after exposure) constitute a simple, relatively safe diagnostic procedure.

F. Allergen inhalation challenge test. When the specific diagnosis remains in doubt because the relevance of a particular exposure is questionable, allergen inhalation or bronchial challenge tests can be used to establish a definitive diagnosis. Various dusts or liquids in the home or workplace can be collected and cultured and extracts prepared from these for inhalation challenge studies in order to identify the responsible antigen. Positive reactions to aerosolized extracts of the appropriate antigen will produce symptoms and signs of hypersensitivity pneumonitis as immediate, late, or dual reactions. However, the patient can become severely ill during the procedure and require hospi-talization and parenteral corticosteroids. Thus, this procedure should **not** be performed routinely and only in laboratories experienced in its administration.

V. DIFFERENTIAL DIAGNOSIS

Both the acute and chronic forms of hypersensitivity pneumonitis can be confused with acute or recurrent pneumonias (viral, fungal, atypical), mycobacterial disease, drug-induced lung disease, organic dust toxic syndrome, ABPA, silo-filler's disease, pulmonary alveolar proteinosis, sarcoidosis, and collagen vascular disease. The latter two are most often accompanied by systemic, medi-astinal, or pleural involvement not found in hypersensitivity pneumonitis. The many causes of interstitial fibrosis, summarized in Table 10-2, can also be confused with chronic hypersensitivity pneumonitis. Although the history and physical as well as radiologic findings can usually differentiate and limit the possibilities, open lung biopsy is justified in puzzling cases or patients without a correlating environmental history.

VI. TREATMENT

A. General treatment measures

1. **Avoidance.** Avoidance of the offending antigen is the most important treatment of hypersensitivity pneumonitis. Alterations in the work and home environment through adjustments in ventilation, heating, airconditioning, and water-based systems may be useful. If avoidance is not possible a trial of masks or dust filters can be attempted. Occasionally, patients must completely avoid the environment in which exposure to the offending agent occurs.
2. **Bronchodilators.** Beta agonists and anticholinergics can alleviate or prevent acute asthmatic symptoms.
3. **Immunotherapy.** Immunotherapy is **not** useful or advisable because of the potential danger that parenteral injection of an antigen might increase levels of precipitins and set the stage for a severe reaction on reexposure to the airborne allergen.

B. Corticosteroid therapy. Corticosteroids are often used when the offending antigen cannot be avoided or when symptoms are severe or prolonged. In the acute episode the response to prednisone 0.5 to 1 mg/kg/day, with a maximum dose of 60 mg/day for a week, with tapering over a month, is often dramatic, with the chest x-ray and spirometric findings (except diffusing capacity) rapidly returning to normal. The chronic form of the disease is more difficult to treat.

A short trial of corticosteroids (prednisone at 0.5 to 1 mg/kg/ day) is usually empirically given with the assumption that part of the interstitial disease is potentially reversible. If improvement is documented, the lowest effective dose should be continued for an extended course. If no improvement is documented prednisone should be discontinued. The use of inhaled corticosteroids (ICSs) is of questionable value in hypersensitivity pneumonitis, although no studies of high-dose or ultra-fine ICSs have been performed.

VII. PROGNOSIS

Provided the antigen is avoided and/or corticosteroid therapy is initiated before irreparable tissue damage (fibrosis) occurs, the prognosis is excellent. In patients with acute disease, avoiding the offending antigen results in a return-to- normal pulmonary function. However, in chronic disease, pulmonary fibrosis and advanced respiratory failure often exist when the patients first present for treatment.

Table 10-2 Principal Causes of Diffuse Interstitial Pneumonitis and Fibrosis

- Chronic aspiration
- Collagen vascular diseases
  - Polymyositis–dermatomyositis
  - Rheumatoid arthritis
  - Scleroderma
  - Systemic lupus erythematosus
- Drugs and medical treatment
  - Antibiotics: nitrofurantoin
  - Antiarrhythmics: amiodarone, tocainide
  - Antiinflammatories: gold, penicillamine
  - Anticonvulsants: phenytoin
  - Bone marrow transplant
  - Chemotherapeutics: azathioprine, bleomycin, busulfan, carmustine (BCNU), chlorambucil, cyclophosphamide, cytosine arabinoside, lomustine (CCNU), melphalan, methotrexate, mitomycin C
  - Dietary supplements: L-tryptophan
  - Dopaminergic drugs: bromocriptine
  - Oxygen
  - Radiation
- Hereditary diseases
  - Familial idiopathic pulmonary fibrosis
  - Lipid storage disorders
  - Neurofibromatosis
  - Tuberous sclerosis
- Hypersensitivity pneumonitis
  - See Table 10-1
- Infections: bacterial, fungal, mycobacterial, viral
- Immune mediated lung diseases
- Eosinophilic granulomatosis
  - Eosinophilic pneumonia
  - Goodpasture's syndrome
  - Sarcoidosis
  - Wegener's granulomatosis
- Gastrointestinal diseases
  - Chronic active hepatitis
  - Cryptogenic cirrhosis
  - Inflammatory bowel disease
  - Primary biliary cirrhosis
- Malignancy: lymphangitic carcinomatosis
- Occupational and environmental exposures
  - Metals: aluminum oxide, antimony, barium, beryllium, cobalt, iron oxide, tin
  - Minerals: asbestos, diatomaceous earth, kaolin, shale, silica, talc
  - Organics: coal, silicone, paraquat, polyvinyl chloride
- Others
  - Adult respiratory distress syndrome
  - Alveolar microlithiasis
  - Alveolar proteinosis
  - Amyloidosis
  - Lymphangioleiomyomatosis
  - Lymphocytic interstitial pneumonitis
  - Histiocytosis X
  - Idiopathic pulmonary fibrosis
  - Mitral stenosis
  - Pulmonary alveolar proteinosis

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

ABPA, the most commonly recognized cause of the allergic bronchopulmonary fungoses, represents an exaggerated immunologic response to fungal colonization of the lower airways. Inflammation in the airways results in subsequent central bronchiectasis, poorly controlled asthma, and frequent exacerbations of asthma or cystic fibrosis (CF). *Aspergillus fumigatus* is the most common causative agent of ABPA, although other *Aspergillus* species and other fungal organisms have been implicated. The prevalence of ABPA is 2% to 15% in patients with C F, 1% to 2% in patients with asthma, and

up to 39% in those asthmatics admitted to the ICU. In the majority of patients, the diagnosis is made after the age of 20 years. The inflammation includes immediate hyper-sensitivity (type I), antigen–antibody complexes (type III), and eosinophil-rich inflammatory cell response (type IVb).

I. CLINICAL PRESENTATION

A. Symptoms and signs. The symptoms from the airway inflammation may be difficult to separate from the underlying difficult-to-control asthma or CF. In fact, with the development of ABPA, the symptoms of asthma or CF typically worsen and may manifest with a new or worsening cough or an increase in sputum production or wheezing. Thick mucus that is tenacious and resistant to suctioning is common. Patients may expectorate brownish plugs or flakes (30% to 60%) and, occasionally, bronchial casts. Patients may variably present with systemic symptoms such as fever, malaise, and weight loss. Physical exam may reveal wheezing or evidence of lobar or segmental collapse from mucous plugging.

B. Laboratory Findings

1. **Peripheral eosinophilia.** Peripheral blood eosinophilia (>1,000/mm^3) is common; however, a low eosinophil count does not exclude ABPA.
2. ***Aspergillus* skin test.** A type I reaction, erythema and edema developing in 1 to 20 minutes, is a characteristic finding of ABPA and represents the presence of *A. fumigatus* specific IgE antibodies. A type III reaction, edema within 6 hours, represents the immune complex hypersensitivity reaction.
3. **Total serum IgE levels.** The total serum IgE level is the most useful test for the diagnosis and follow-up of ABPA. A normal IgE level excludes ABPA from the differential. Total IgE levels decrease with the use of glucocorti-coids, and a 35% to 50% decrease in total levels is interpreted as disease remission. A doubling of IgE levels may indicate relapse of disease.
4. **Serum *A. fumigatus*–specific IgE and IgG antibodies.** An elevated level of *A. fumigatus*–specific IgG or IgE antibodies measured by fluorescent enzyme immunoassay (*Aspergillus* EIA) is characteristic of ABPA, but nonspecific.
5. **Serum precipitins against *A. fumigatus***. The precipitating IgG antibodies are elicited from crude extracts of *A. fumigatus* and are demonstrated by a double gel diffusion technique. These can be seen in other lung disease and are therefore supportive but not diagnostic of ABPA.
6. **Sputum culture.** A sputum culture growing *A. fumigatus* is supportive but not diagnostic for ABPA as the fungus is ubiquitous in the environment and can be seen in other lung conditions.

C. Radiographic findings. A wide spectrum of radiographic findings is seen in ABPA. Mucoid impaction of involved airways frequently results in segmental or lobar atelectasis that is visualized as transient or fixed pulmonary infiltrates. Central or proximal bronchiectasis with normal tapering of the distal airways is specific for ABPA. Impaction of dilated bronchi is classically described as “finger-in-glove” projections. Tram tracking, which represents thickened bronchial walls, is also described. HRCT has a higher specificity and sensitivity in detecting central bronchiectasis than plain x-rays. Common HRCT findings include central

bronchiectasis, mucus plugging consolidations, centrilobular nodules with tree-in-bud opacities, bronchial wall thickening, atelectasis, and mosaic perfusion with air trapping on expiration. Upper lobe fibrosis occurs in patients with chronic disease.

D. Physiologic tests. The presence of mucus plugging (mucus impaction syndrome) and airway damage is commonly, but not always, associated with evidence of reversible airways obstruction and lowered diffusing capacity on pulmonary function testing. This may wax and wane depending on the changing mucous obstruction. A restrictive ventilatory pattern may occur with pulmonary fibrosis, as a result of longstanding disease, and may not reverse with corticosteroid therapy.

II. IMMUNOLOGIC FEATURES

Persistence of *Aspergillus* organisms in the lung results in the formation of hyphae, which release antigens that compromise mucociliary clearance, breach the airway epithelial barrier, and activate the innate immunity of the lung. The result is an influx of inflammatory cells leading to an early- and late-phase inflammatory reaction. These antigens are presented to T cells with resultant activation of Th2 $CD4^+$ T-cell responses. The T-cell response causes a release of cytokines (interleukin [IL]-4, IL-5, and IL-13), which leads to a total and *A. fumigatus*–specific IgE synthesis, mast cell degranulation, and activation of a strong eosinophilic response. Skin tests positive for *Aspergillus* show both an immediate wheel-and-flare reaction (type I) and a late reaction of erythema and edema (type III).

III. PATHOLOGIC FEATURES

The pathology of ABPA can vary from patient to patient and even within a single patient. Common histologic findings within affected bronchi include mucus, fibrin, Curschmann's spirals, Charcot-Leyden crystals, and inflammatory cells (notably eosinophils within noncaseating granulomas, bronchial walls, and peri-bronchial parenchyma). Although thick, tenacious mucous plugs with fungal elements fill the affected bronchi, the organism does not invade the bronchial wall or lung parenchyma. In some patients, the bronchial wall damage is associated with intense parenchymal infiltration by eosinophils and mononuclear cells and the presence of granulomas (bronchocentric granulomatosis). Subsequently, proximal cystic bronchiectasis and upper lobe fibrosis develop. Bronchiectatic cavities can often show the scant hyphae of *Aspergillus*. Patients can often show a pattern of organizing pneumonia similar to that of bronchiolitis obliterans.

IV. DIAGNOSTIC APPROACH

There is no individual test to establish the diagnosis of ABPA, and the diagnosis is usually confirmed by the use of clinical, radiographic, and immunologic criteria. Diagnosis may be complicated by recent steroid use, as it will alter skin reactivity to *Aspergillus* antigens, serum total IgE levels, and peripheral blood eosinophilia levels. If the diagnostic criteria are not met but there is a high level of suspicion for the diagnosis of ABPA, the studies can be repeated when the patient has been off of steroids for a sufficient amount of time.

A. Specific etiologic approach. The diagnosis is certain if the following conditions (usually present in over 90% of the patients) are present. The presence or absence of central bronchiectasis classifies ABPA as Seropositive-ABPA (ABPA-S) or ABPA with central bronchiectasis (ABPA-CB).

1. **Asthma (episodic bronchial obstruction) or CF with acute or sub-acute deterioration**
2. **Immediate skin test reactivity to *Aspergillus* antigens**
3. **Serum total IgE levels > 1,000 ng/mL**
4. **Elevated specific serum IgE and IgG to *A. fumigatus***
5. **In addition for ABPA-CB: central bronchiectasis**
6. **Additional findings:**

Mucous plugs.
Aspergillus on culture of sputum
Precipitating antibodies to *A.* fumigatus (may be considered a diagnostic criteria in CF).
Transient or fixed pulmonary infiltrates (for CF a change in radiographic findings may be considered a diagnostic criteria)
Delayed skin test reactivity to *Aspergillus* antigens.

V. DIFFERENTIAL DIAGNOSIS

Patients with ABPA frequently have had a prior diagnosis of problematic asthma, C F, chronic bronchitis, recurrent pneumonia, tuberculosis, or bronchiectasis from other causes. However, it is possible for some of these entities to coexist with the fungal hypersensitivity. ABPA may be confused with other conditions exhibiting pulmonary infiltrates with eosinophilia (Table 10-3).

Table 10-3 Eosinophilic Syndromes with Pulmonary Involvement

Syndrome	Etiology	Symptoms	Physical Findings	Blood Eosinophilia	Chest x-Ray	Other Features	Treatment	Prognosis
Simple pulmonary eosinophilia (Loeffler's syndrome)	Drugs, parasites, and others	None or mild cough, fever, myalgia	None or minimal	10%–30%	Transient, migratory, pleural-based infiltrates		None, usually self-limited	Excellent
Chronic (prolonged) pulmonary eosinophilia	Majority unknown, drugs parasites	Fever, sweats, cough, dyspnea, wheezing, weight loss	Wheezes	20%–40% in two-thirds of patients	Dense peripheral infiltrates, recur in same location	Restriction on PFTs, may present with asthma	Corticosteroids	Good with prolonged therapy
Tropical eosinophilia	Filarial parasites	Dry cough, dyspnea, nocturnal wheezing, malaise, weight loss	Crackles, wheezes, lymphadenopathy in children	20%–50%	Increased markings, 1–3 mm nodules or mottled opacities	IgE > 1,000 u/mL, antifilarial antibodies	Diethylcarbamazine	Good
Churg-Strauss syndrome and polyarteritis nodosa	Unknown	Wheezing, fever, weight loss, fatigue, neuropathy, sinus disease	Wheezes	>10% in Churg-Strauss, >20% in 20%–30% of PAN	Transient patchy infiltrates, consolidations, nodules, effusions	Vasculitis of small and medium arteries	Corticosteroids, cyclophosphamide	Poor
Eosinophilia–myalgia syndrome	Contaminants in L-tryptophan	Cough, dyspnea, myalgias, fatigue	Wheezes, peripheral edema	>1,000/mm^3	Interstitial and reticulonodular infiltrates		Corticosteroids, cessation of tryptophan	Fair

VI. TREATMENT

The goal of treatment is to prevent the progression of disease by controlling the inflammatory component of the asthma and suppressing the immune response to the fungus.

A. Corticosteroids

1. **Dose.** There is no standard recommended dose of corticosteroids in ABPA. Oral prednisone at 20 to 40 mg/day or 0.5 mg/kg/day is an appropriate choice. The efficacy of alternate-day corticosteroids or ICSs is limited since asymptomatic pulmonary infiltrates can continue to develop during either kind of therapy.
2. **Response.** The goal of corticosteroid therapy is to reduce the total serum IgE levels by 35 to 50%. At this level of total serum IgE reduction, symptoms and radiographic improvement follow within days to weeks. Once total serum IgE reduction is achieved, one should check total serum IgE levels frequently to establish a baseline value.
3. **Duration.** A 6-month course of prednisone therapy with subsequent tapering and monitoring (by history, chest x-ray, and serum IgE levels) will suffice in most patients. However, in some patients, the disease may be exacerbated after corticosteroids are discontinued, and after repeated courses, they may require prednisone therapy indefinitely (e.g., at least 10 mg/day).

B. Antifungal therapy. Although the data are still limited, the use of anti-fungals, specifically itraconazole, to eradicate or reduce fungal colonization may decrease the steroid dose needed to control the disease and decrease the risk of relapse. The suggested dose of itraconazole is 200 mg bid for 16 weeks, based on a study of 55 subjects. Voriconazole is also used clinically, given its improved tolerance profile and bioavailability over itraconazole; however, its comparative efficacy in ABPA is unknown.

C. Monoclonal antibody against IgE (omalizumab). Anti-IgE therapy (omalizumab) has been tried experimentally but is limited by the very high IgE levels seen in ABPA and potential toxicity.

VII. PROGNOSIS

Pulmonary infiltrates and further lung destruction continue to develop in untreated patients. Irreversible bronchiectasis, pulmonary fibrosis, recurrent pneumonias, and, eventually, respiratory failure result. However, early and effective treatment with corticosteroids is associated with significantly fewer recurrences of pulmonary infiltrates and less bronchial damage. Fungal invasion or extension in patients on long-term corticosteroid therapy has not been documented.

EOSINOPHILIC LUNG DISEASE

Eosinophilic lung disease is a generic term applied to a broad group of eosinophilic syndromes with pulmonary involvement. In this section, simple pulmonary eosino-philia (Löffler's syndrome), chronic eosinophilic pneumonia, tropical eosinophilia, and pulmonary eosinophilias with vasculitis (Churg-Strauss syndrome [CSS] and polyarteritis nodosa [PAN]) will be discussed (see Table 10-2). ABPA, another member of this spectrum of diseases, is discussed separately.

I. SIMPLE PULMONARY EOSINOPHILIA (LöFFLER'S SYNDROME)

Löffler's syndrome is a constellation of mild pulmonary and systemic symptoms with peripheral eosinophilia. It is usually a response to an infectious or drug exposure and remits spontaneously.

A. Clinical presentation. Patients are usually asymptomatic or have mild cough, wheeze, and/or constitutional symptoms such as low-grade fever and myalgias. The syndrome likely represents a hypersensitivity response to one of numerous causative agents (para-aminosalicylic acid, sulfonamides, chlorpropamide, nitrofurantoin, phenytoin, bleomycin, tetracycline, nickel carbonyl, *Ascaris* and *Strongyloides* parasites, and several others), and a careful history of exposure can be important in establishing the diagnosis. Idiopathic cases also occur.

B. Laboratory findings. Peripheral blood eosinophilia is present in the range of 10% to 30%. Chest x-ray documents nonsegmental, bilateral or unilateral, transient, and migratory infiltrates, which may be interstitial or alveolar. Stool examination can reveal parasites in cases due to *Ascaris* and *Strongyloides*. Although rarely required, biopsies show interstitial eosino-philic pneumonia without evidence of necrosis or vasculitis.

C. Diagnostic approach. No single feature establishes the diagnosis. A mildly symptomatic patient with eosinophilia, transient pulmonary infiltrates, and spontaneous resolution within a month meets the diagnostic criteria. An exposure history is helpful.

D. Treatment and prognosis. Simple pulmonary eosinophilia most often resolves spontaneously within a month of the onset of symptoms. Eliminating exposure to the offending agent, or treatment of the parasitic infection, is usually curative. A brief tapering course of prednisone may be required for more severe cases. The prognosis for a complete recovery is excellent.

II. CHRONIC EOSINOPHILIC PNEUMONIA

Chronic eosinophilic pneumonia is a pulmonary and systemic disease generally affecting females in their fifth decade. The symptoms are insidious in onset, and time to diagnosis from onset of symptoms is, on average, 7 months. Peripheral eosinophilia may or may not be present. While some cases are due to the same agents associated with simple pulmonary eosinophilia, the etiology remains unknown in the majority of cases.

A. Clinical presentation. Patients present with moderate to severe symptoms including cough, fever, dyspnea, weight loss, sputum production, sweats, malaise, and wheezing that have lasted for more than 1 month. A history of preexisting atopy is elicited in more than one-half of the cases, and new-onset asthma can be the presenting symptom. Asthma can persist even after treatment.

B. Laboratory findings. Peripheral blood eosinophilia is present in two-thirds of patients. Chest x-ray shows progressive dense infiltrates that do not conform to lobar or segmental anatomy and are characteristically subpleural. This peripheral "butterfly" distribution, also described as the photographic negative of pulmonary edema, may be difficult to appreciate on some chest x-rays but is universally documented by computed tomography (CT) scan of the chest. Opacities may disappear and recur in exactly the same location over time. Pulmonary function tests exhibit a restrictive ventilatory defect with a reduction in the diffusing capacity. Hypoxemia is noted on blood gases. Lung biopsy confirms the presence of eosinophils and mononuclear cells within the alveoli and interstitium. Occasionally, granuloma formation with eosinophilic abscesses and microangiitis occur. Twenty-five percent of patients will have bronchiolitis or bronchiolitis obliterans. Fibrosis, if present, is minimal.

C. Diagnostic approach. The finding of appropriate clinical symptoms and a characteristic chest x-ray is diagnostic in 75% of cases. The diagnosis is often made by radiographic findings alone. High levels of peripheral eosin-ophilia are confirmatory but are not present in one-third of cases. BAL usually shows greater than a 25% eosinophilia. Lung biopsy may be required in the rare cases that lack characteristic chest x-rays or chest CT scans.

D. Treatment and prognosis. Early treatment is essential as <10% of chronic eosinophilic pneumonias resolve spontaneously and deaths have been reported. Therapy should begin with 30 to 60 mg/day of **prednisone** (1 to 2 mg/kg/day in children) with gradual tapering and maintenance on an individual basis. The clinical, x-ray, and histologic response is often dramatic and occurs within days, but relapses can occur if corticosteroids are decreased prematurely. No studies have yet been performed with high-dose inhaled steroids. The optimal duration of therapy is unknown, and indefinite maintenance therapy may be necessary in difficult cases. Treatment or avoidance of the underlying cause, if known, is critical, as for simple pulmonary eosinophilia. Inhaled bronchodilators should be used to treat any bronchospastic component. The prognosis is good, but protracted therapy may be needed.

III. ACUTE EOSINOPHILIC PNEUMONIA

Acute eosinophilic pneumonia (AEP), a distinct entity from chronic eosinophilic pneumonia, is typically characterized by acute respiratory failure with peripheral and pulmonary eosinophilia, and dense pulmonary infiltrates. AEP typically occurs in the third to fifth decades of life and affects men more often than women. The exact etiology of AEP is unknown, but cases are usually reported after exposure to environmental antigens and in association with cigarette smoking.

A. Clinical presentation. Patients present with an acute febrile illness of <3 weeks duration along with nonproductive cough and dyspnea. Symptoms can be quite severe and result in respiratory failure. Physical exam reveals fevers, tachycardia, and, frequently, severe hypoxemia. Pulmonary exam reveals crackles and wheezes, predominantly in the basal regions.

B. Laboratory findings. Routine laboratory tests are nonspecific and of little utility. Erythrocyte sedimentation rates are usually elevated. IgE levels are elevated in a majority of patient, and peripheral eosinophilia may be found as the disease progresses. Chest radiograph reveals diffuse bilateral alveolar and reticular opacities. HRCT reveals bilateral patchy ground glass opacification or reticular opacities. Unlike chronic eosinophilic pneumonia, the opacities are not localized to the peripheries of the lung fields. Pulmonary function tests demonstrate restrictive defect with impaired diffusion. Bronchoalveolar lavage (BAL) cell count and differential typically has >25% eosinophils, and the proportion of lymphocytes and neutrophils is increased above normal. Histopathology shows a marked number of interstitial and alveolar eosinophils. Acute and organizing diffuse alveolar damage is also common.

C. Diagnostic approach. A diagnosis of AEP can be made without histopathologic confirmation in the appropriate clinical setting with prominent BAL eosinophilia and without other known causes of pulmonary eosinophilia. Transbronchial biopsy is insufficient to make a diagnosis due to limited sample size, but open lung biopsy is rare in these patients.

D. Treatment and prognosis. Although spontaneous improvement has been reported, most patients progress to respiratory failure, and immediate treatment with corticosteroids is necessary. Initial

treatment with prednisone 40 to 60 mg/day is appropriate. If respiratory failure is present, methylpred-nisolone 60 to 125 mg intravenously every 6 hours until respiratory failure resolves (usually 1 to 3 days) may be indicated. Response to steroids is dramatic, and relapse after withdrawal of steroids is rare. High-dose steroids should be continued for 2 weeks after resolution of symptoms and then tapered off over the course of 3 months.

IV. TROPICAL EOSINOPHILIA

Tropical eosinophilia occurs in patients infected with the filarial parasites *Wuchereria bancrofti* and *Brugia malayi*. The filaria is transmitted through mosquitoes, and the adult worm will eventually live in the lymphatic system and release microfilaria. The microfilaria travels to the lung and causes a marked inflammatory reaction. Patients are typically males (4:1 sex ratio) in their third or fourth decade and originate from or have prolonged travel to endemic areas such as India, Africa, South America, and Southeast Asia.

A. Clinical presentation. Patients usually have an insidious onset of dry cough, dyspnea, nocturnal wheezing, malaise, anorexia, and weight loss. Coarse crackles and wheezes are present during symptomatic episodes. Moderate lymphadenopathy and hepatomegaly are common in children but not in adults.

B. Laboratory findings. The eosinophil count is extremely high (>20% to 50% and >3,000/mm^3) and persists for weeks. IgE levels are elevated (>1,000 IU/mL), and high levels of antifilarial antibodies are present in both serum and bronchial lavage specimens. No microfilaria is seen because the parasite is sequestered in the lung parenchyma. BAL reveals up to a 50% eosinophilia. Chest x-rays demonstrate increased bronchovascular markings and diffuse 1- to 3-mm nodules or mottled opacities. Pulmonary function tests show a restrictive ventilatory pattern and diffusing capacity impairment. Obstructive ventilatory defects are also seen in 25% to 30% of patients. Biopsy findings include eosinophilic bronchopneumonia with eosinophilic abscesses and interstitial granulomas surrounding degenerated microfilaria or areas of necrosis.

C. Diagnostic approach. The diagnosis is usually made on clinical grounds in a patient that has had protracted exposure to an endemic area. The combination of diffuse nodular changes on chest x-ray, extreme eosinophilia, and high levels of serum IgE are important findings; a rapid response to treatment confirms the diagnosis. High titers of antifilarial antibodies are present but are not specific for the disease.

E. Treatment and prognosis. Tropical eosinophilia requires specific treatment with diethylcarbamazine (6 mg/kg/day divided into 3 doses) for 14 to 21 days. Doxycycline 200 mg/day for 8 weeks is also effective. Responses to therapy are generally rapid and associated with notable improvement in pulmonary function; however, 10% to 20% of patients either relapse or have unsatisfactory long-term responses. Another course of treatment is indicated in these cases, but some patients may still progress to chronic interstitial fibrosis.

V. CHURG-STRAUSS SYNDROME AND POLYARTERITIS NODOSA

CSS and PAN are rare systemic diseases with several overlapping characteristics. Both are forms of systemic vasculitis that involve small and medium vessels and can be associated with peripheral eosinophilia and pulmonary involvement. They are described together to highlight

these similarities as well as their differences. While CCS occurs in patients with a long-standing history of allergic disease (asthma, sinusitis, or rhinitis), PAN is not associated with an atopic background but rather with prior infection by Hepatitis B. Almost all patients with CSS have pulmonary involvement and peripheral eosinophilia, while PAN rarely affects the lungs and most often presents without eosinophilia. Both conditions affect men and women of all ages.

A. Clinical presentation. In CSS, patients with a known history of asthma usually present with paranasal sinus disease, mono- or polyneuropathy, and constitutional symptoms of fever, weight loss, and fatigue. Involvement of additional organs with vasculitis is common (e.g., skin [70%], gastrointestinal [59%], renal [49%], cardiac [47%], and central nervous system [27%]), although overt renal failure is rare. Several medications have been associated with the appearance of CSS (leukotriene receptor antagonists, glucocorticoids, and omalizumab). This is more likely related to the unmasking of preexisting disease rather than a specific reaction to the medication. However, cases of CSS have been reported in patients treated with leukotriene receptor antagonists in the absence of steroid use or withdrawal, and the relationship between this class of medications and CSS should be recognized by clinicians. As in CSS, patients with PAN present with systemic symptoms including fever, fatigue, and weight loss as well as complaints related to specific organ system involvement including mononeuritis multiplex, skin rash, renal disease, mesenteric arteritis, liver insufficiency, coronary artery disease, and orchitis. However, as stated, lung involvement occurs in <10% of PAN cases.

B. Laboratory findings. In CSS, eosinophilia (>10%) is present in 95% of subjects, whereas in PAN, eosinophilia is seen in only 20% to 30% of cases. In CSS, there is also an elevated BAL eosinophil count in one-third of subjects. Because of the systemic vasculitis, these patients also commonly have anemia, leukocytosis, elevated erythrocyte sedimentation rates, elevated serum IgE levels, hypocomplementemia, and decreased renal function. P-ANCA is positive in 35% to 50% of CSS but is negative in PAN. Radiographic abnormalities are almost always present in CSS and include transient patchy infiltrates, consolidations, pleural effusions, and nodules that rarely cavitate. High-resolution chest CT can demonstrate irregular pulmonary artery aneurismal changes as well scentrilobular and perivascular nodules. Lung biopsy in CSS is associated with eosinophilic vasculitis of small- and medium-sized arteries and veins with perivascular necrotizing granulomas and eosinophilic infiltrates. Biopsies in PAN demonstrate vasculitic changes limited to small and medium arteries only.

C. Diagnostic approach. Diagnostic criteria established by the American College of Rheumatology for diagnosing CSS include patients who exhibit at least four of six well-defined criteria: (1) asthma, (2) eosinophilia > 10%, (3) mono- or polyneuropathy, (4) nonfixed pulmonary infiltrates, (5) para-nasal sinus abnormalities, and (6) extravascular extension of eosinophils on lung biopsy. Open lung biopsies are usually required as transbronchial biopsies rarely yield adequate tissue. In contrast, PAN does not occur in subjects with preexisting asthma and is a multiorgan vasculitis in most cases. The diagnosis of PAN is made by fulfilling at least three of the ten following criteria: (1) weight loss of at least 4 kg; (2) livedo reticularis; (3) testicular pain or tenderness; (4) myalgias, weakness, or tenderness; (5) mononeuropathy or polyneuropathy; (6) diastolic blood pressure >90 mm Hg; (7) elevated blood urea nitrogen; (8) hepatitis B virus infection; (9) arteriographic abnormalities; and (10) biopsy specimen of small or medium-sized artery containing polymorphonuclear leukocytes. Both CSS and PAN should be

confirmed by biopsy of an affected organ, not necessarily the lung.

D. Treatment and prognosis. High doses of corticosteroids (**prednisone** 1 mg/kg/day for the first 2 months) are initially required in treating both Churg-Strauss and PAN and are tapered according to clinical improvement. **Cyclophosphamide** (2 mg/kg/day adjusted for neutropenia) added with prednisone at the beginning of treatment induces remission more rapidly and reduces the incidence of relapse. However, because of a greater morbidity from infectious complications, cyclophosphamide should be reserved for those patients that respond too slowly or relapse on prednisone alone. With treatment, patient survival in CSS has been reported as high as 93% to 94% at 1 year and 60% to 97% at 5 years, and at 80% at 5 years in PAN. The following five factors, when present at diagnosis, are associated with poorer prognosis: cardiomyopathy, central nervous system involvement, severe gastrointestinal symptoms, renal failure (i.e., creatinine > 1.58 mg/dL), and high proteinuria (>1 g/day).

VI. DIFFERENTIAL DIAGNOSIS OF PULMONARY DISEASE AND EOSINOPHILIA

The combination of pulmonary infiltrates and eosinophilia (of the blood or tissue) raises a broad differential, which includes the eosinophilic diseases in this section, ABPA, drug reactions, a multitude of infectious processes including varied parasitic infections (*Strongyloides*, *Ascaris*, *Ancylostoma*, *Toxocara*, and others), mycobacterial and fungal infections, and brucellosis, malignancy, or collagen-vascular diseases, which are occasionally associated with the hypereosinophilia syndrome, and less likely with Wegener's granulomatosis. A detailed history and physical exam including special attention to a history of asthma or atopic disease, travel and exposures, and drug use is invaluable. This coupled with radiographic data and properly selected serology studies can lead to a diagnosis. Occasionally BAL or even open lung biopsy may be necessary. Biopsies in organs other than the lung may be necessary in varied collagen vascular diseases.

VII. IMMUNOLOGY OF THE EOSINOPHILIC LUNG DISEASES

The exact immunologic mechanisms responsible for eosinophilic lung disease are not known. Recent animal and human studies clearly suggest that these syndromes are T lymphocyte mediated and that selective secretion of IL-4 and IL-5 by helper lymphocytes are responsible for the specific increases in serum IgE and eosinophils, respectively. The eosinophil undoubtedly plays a role in protection against parasites but also likely plays a significant role in the inflammation and tissue injury observed in patients with eosinophilic lung disease. Stimulated eosinophils release granule-derived factors, including major basic protein (toxic for parasites, tumor cells, and respiratory cells and which functions as a mast cell activator), eosinophilic cationic protein (toxic for parasites and nerve cells and also is a mast cell activator) and eosinophil-derived neurotoxin. Stimulated eosinophils also release membrane-derived mediators including LTC_4, LTD_4, and PAF.

Antiglomerular Basement Membrane disease

Goodpasture's syndrome is one of the first diagnostic considerations in the patient with pulmonary hemorrhage and nephritis. Its immunopathologic nature is underscored by its more accurate name, antiglomerular basement membrane disease (anti-GBM). Although Goodpasture originally

described the syndrome as a sequelae of influenza, it is now well accepted as an antigen–antibody reaction (type II) against the alpha-3 chain of type IV collagen. This is a rare disease that typically affects males (male to female ratio 7:1) in their second to third decade of life, with occasional familial occurrence. There is also an atypical form, which affects elderly females and has a renal predominance. Affected patients are usually smokers.

I. CLINICAL PRESENTATION

A. Symptoms and signs. Hemoptysis, ranging from mild to life-threatening, is present in more than 90% of patients. Clinical manifestations of renal disease are often concurrent with, but may precede, hemoptysis. Occasionally, there are only renal manifestations, while less often (<10%) lung involvement will occur without renal disease. Other symptoms include dyspnea, fatigue, cough, chest pain, fever, and weight loss. Physical findings commonly include pallor, crackles and wheezes, edema, and occasionally mild hypertension and retinal hemorrhages and exudates.

B. Laboratory findings. ELISA and indirect immunofluorescence for serum antiglomerular basement membrane antibodies are sensitive and relatively specific tests for anti-GBM disease. Up to one-third of patients may be P-ANCA positive. ESR is normal or minimally elevated. Iron-deficiency anemia is present in a majority of patients. Other laboratory findings include proteinuria, red and white blood cell and granular casts, leukocyto-sis, and progressive azotemia. The urinalysis may be initially normal in up to 10% of patients.

C. Radiographic findings. Following pulmonary hemorrhage, the chest x-ray will initially show widespread bilateral patchy airspace consolidation that simulates pulmonary edema or opportunistic infection in 90% of cases. Serial chest x-rays show either progressive acinar consolidation during continued pulmonary hemorrhage or a reticular pattern with a distribution that parallels the airspace process, or both. The chest x-ray findings may return to normal within days of the acute episode. Progressive interstitial fibrosis results from repeated hemorrhage and increasing hemosiderin deposition within the lung interstitium.

D. Pulmonary function tests. Pulmonary function tests often reveal a restrictive ventilatory defect. In the absence of recent hemorrhage, the diffusing capacity is reduced. With acute hemorrhage, blood is sequestered in the alveolar space where it can bind the test gas (carbon monoxide) and artificially raise the diffusing capacity by 30% or more above the usually reduced baseline.

II. IMMUNOLOGIC FEATURES

Anti-GBM antibodies are directed against the carboxy-terminal region of the alpha-3 chain of type IV collagen. It is postulated that alteration of the three-dimensional structure of collagen following an infectious or toxic exposure unveils this epitope and plays an important role in the initiation of the antibody response. This may explain the higher incidence of disease seen after viral infections and drug exposures. Once formed, anti-GBM antibody binds to the renal glomeruli, where subsequent fixation of complement and the attraction of neutrophils result in the characteristic renal pathology. Unlike the kidney, the lung is not directly damaged by circulating antibody as the fenestrations in the basement membrane of the lung are not large enough to admit an IgG protein. It is not until a second insult occurs that there is an increased alveolar–capillary

leak. This may explain the higher incidence of anti-GBM disease in smokers. There is a higher incidence of disease in patients with HLA-DR2, especially with the DRw15 haplotype and with HLA-B7. This may be due to alterations in antigenic processing by B cells, macrophages, and dendritic cells with these phenotypes.

III. PATHOLOGIC FEATURES

A. Lungs. The lungs reveal diffuse alveolar hemorrhage during an acute episode. Light microscopy reveals hemosiderin-laden macrophages, intact alveolar and endothelial cells, and a component of interstitial fibrosis in patients with chronic disease. Vasculitic changes are absent or minimal, but electron microscopy shows vascular damage with wide endothelial gaps and occasionally fragmentation of basement membranes. Immunofluorescence demonstrates linear deposits of IgG and, often, complement bound to the basement membranes of alveoli.

B. Kidneys. Renal biopsy shows focal and segmental glomerulonephritis with crescent formation and diffuse glomerular necrosis that progresses to interstitial inflammation and glomerular fibrosis without vasculitis. Electron microscopy reveals endothelial cell proliferation and swelling, increased basement membrane material, and fibrin deposition beneath the capillary endothelium. Linear deposits of IgG antibody along the capillary basement membranes demonstrated by immunofluorescence are seen more often in the kidney than in the lung. Deposition of IgA and IgM has also been reported.

IV. DIAGNOSTIC APPROACH

A. Presentation. Anti-GBM disease is diagnosed by the presence of pulmonary hemorrhage, glomerulonephritis, and circulating antiglomerular basement antibodies. Renal and pulmonary involvement may not manifest concurrently, which complicates the diagnosis.

B. Confirmation

1. **Renal biopsy** with immunofluorescence microscopy is the mainstay of diagnosis and should be performed with the first manifestations of kidney involvement to establish an early diagnosis as well as to determine the extent and severity of damage.
2. **Serum anti-GBM.** Serologic testing using direct enzyme-linked immuno-assay (ELISA) kits for anti-GBM antibody are reliable and sensitive tests for anti-GBM disease and are useful in following the response to treatment. Western blot can be used for confirmation of a positive ELISA. These tests may take several days to return from reference laboratories and should not delay treatment. There have been reports of false positive anti-GBM antibody in HIV-negative patients with PCP, although the anti-GBM was not directed to the alpha carboxy portion of the protein.
3. **Lung biopsy.** Transbronchial lung biopsy can be helpful if sufficient alveoli are obtained but has a lower yield than percutaneous renal biopsy and is difficult to perform serially for follow-up.

V. DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes exposure to trimellitic anhydride, hydrocarbons, mitomycin C, penicillamine, or smoked crack cocaine. Other considerations include microscopic polyangiitis, Wegener's granulomatosis, systemic lupus erythematosus, Henoch-Schonlein purpura, CSS, pulmonary capillaritis, idiopathic pulmonary hemosiderosis, uremic pneumonitis, acute (poststrep-tococcal) glomerulonephritis, and pneumococcal or viral pneumonia with nephritis. Several cases of pulmonary–renal disease similar to anti-GBM disease but without anti-GBM antibodies have been reported and presumably involve other immunopathologic mechanisms.

VI. TREATMENT

A. General measures. Emergency stabilization with blood transfusions, correction of fluid and electrolyte imbalances, supplemental oxygen, intubation and mechanical ventilation, and hemodialysis is often necessary.

B. Plasmapheresis. Although there is no clear data supporting the use of plasma-pheresis, it is biologically plausible that removing anti-GBM antibodies could ameliorate the consequence of the disease. Current treatment recommendations are to start early plasmapheresis of 4 L every day or every other day for 2 to 3 weeks, after which time the patient's need for plasmapheresis can be reevaluated. Plasmapheresis should occur in conjunction with immunosup-pressive therapy. However, this therapy should be reserved for patients who are not dialysis dependent as there are few data to show positive response in these patients and, thus, the risks may outweigh the benefits.

C. Immunosuppressive therapy. The current treatment of choice is an aggressive combination of corticosteroids and cyclophosphamide, given the high likelihood of morbidity and mortality associated with this disease.

1. **Corticosteroids.** Steroid therapy consists of methylprednisone 15 to 30 mg/kg/day intravenously for 3 days, followed by prednisone 1 mg/kg/ day. This can be tapered once remission is induced.
2. **Cyclophosphamide.** The initial cyclophosphamide dose is 2 mg/kg/day intravenously. Oral cyclophosphamide can also be used, but its comparative efficacy to intravenous cyclophosphamide has not been established.

D. Duration of therapy. Double immunosuppression should be continued until circulating anti-GBM antibody is no longer detectable and renal function has stabilized. This is usually accomplished in 2 to 3 months. Thereafter, maintenance therapy with less toxic regimens such as azathio-prine and low-dose prednisone versus prednisone alone should be continued until anti-GBM antibodies have been negative for 6 to 9 months. With treatment, chest x-rays and pulmonary function tests may return to normal in days to weeks, whereas renal function either improves or progresses to end-stage disease depending on the presenting severity of renal damage.

VII. PROGNOSIS

Prognosis appears to be related to the severity of renal disease at presentation as reflected by serum creatinine levels and percentage of crescent involvement on renal biopsy. No therapy, or brief immunosuppressive therapy alone, results in end-stage renal disease in up to 75% of

patients and death from pulmonary hemorrhage in 20% to 50%. Since antibody production is short-lived due to T-cell regulatory mechanisms, relapses are rare.

WEGENER'S GRANULOMATOSIS

Wegener's granulomatosis is a necrotizing granulomatous vasculitis classically involving the upper and lower respiratory tracts and often the kidneys. It is one of the most common vasculitides involving the lung, with a prevalence of 3/100,000. **Generalized** Wegener's granulomatosis is the term given when the manifestations are truly systemic and is the most common form of the disease. In a minority of cases (<20%), the disease appears to be limited to either the upper airways and lungs, or lungs alone, indicating **limited** Wegener's granulomatosis. Wegener's granulomatosis can occur at any age (reported cases from 9 to 78 years) but most commonly affects patients in the fourth and fifth decades of life. There is no sex predilection although affected persons tend to be white.

I. CLINICAL PRESENTATION

A. Symptoms and signs. Wegener's granulomatosis can involve virtually any organ system with vasculitis and/or granulomatous changes.

1. **Respiratory.** Over 90% of patients seek medical attention because of upper and/or lower respiratory symptoms including sinusitis (50%), nasal complaints (36%), otitis media (25%), hearing loss (15%), cough (19%), hemoptysis (12%), and pleuritis (10%). About 92% of patients eventually develop ear, nose, or throat involvement, and 85% develop lung disease.
2. **Renal.** While glomerulonephritis eventually develops in 75% to 80% of cases, it is rarely the cause of presenting symptoms.
3. **Other.** Musculoskeletal symptoms are prominent in two-thirds of patients, eye involvement in 50%, fever at some point in 50%, and skin lesions such as palpable purpura, ulcers, or nodules in 40% to 50%. 35% develop weight loss. About 5% to 15% of patients will develop symptoms from pericarditis, central nervous system mass effects, retro-orbital pseudotumors, or mononeuritis multiplex.

B. Laboratory findings

1. **Antineutrophil cytoplasmic antibody (ANCA).** Serum from 88% to 95% of patients with active systemic disease tests positive for diffuse granular cytoplasmic immunofluorescent staining of neutro-phils **(C-ANCA)**, which is highly specific for the diagnosis. This is reduced to approximately 50% in the limited form of the disease. A minority of patients test positive for perinuclear staining (P-ANCA), which occurs in other vasculitides and is not diagnostic for Wegener's granulomatosis. Antineutrophil cytoplasmic antibodies can also be detected by ELISA assay with specificity directed against either the serine proteinase 3 antigen (Pr3-ANCA), which correlates primarily with C-ANCA (90% of the time), or with specificity against myeloperoxidase (MPO-ANCA), which correlates primarily with P-ANCA immunofluorescence. The 1999 International Consensus Statement on Testing and Reporting of ANCA recommends that both neutrophil immunofluorescence and ELISA assays be performed in patients with suspected Wegener's granulomatosis since 5% to 10% of patients are positive for only one assay

and not the other. C-ANCA and Pr3-ANCA titers parallel disease activity in only about 50% of patients and should not be used as the sole indicator to monitor disease or predict relapses.

2. **Blood and urine.** Anemia with normal indices, leukocytosis, throm-bocytosis, hypergammaglobulinemia (particularly IgA and IgE), and an elevated Western erythrocyte sedimentation rate are characteristically found before treatment. Peripheral eosinophilia, antinuclear antibodies, and cryoglobulinemia rarely occur, and complement levels are normal or elevated. Elevated BUN and creatinine are common as are proteinuria, hematuria, and increased urinary sediment.

C. Radiographic findings. Chest x-ray changes occur in 85% of cases but are often fleeting and asymptomatic. Unilateral or bilateral lung infiltrates are the most common finding (63%), followed by unilateral or bilateral nodules (31%). Cavitation of the nodules can occur. CT of the chest will better delineate the x-ray findings. Nodules may be seen perivascularly. Sinus x-rays or CT will also be abnormal at some point in up to 85% of cases.

D. Physiology studies: PFTs are variable in Wegner's granulomatosis and can show either a restrictive defect with a decreased diffusion capacity or an obstructive defect due to endobronchial involvement.

II. IMMUNOLOGIC FEATURES

The target antigen of C-ANCA is serine protease 3 (Pr3), a component of the azurophilic neutrophil granule. *In vitro*, exposure of neutrophils to ANCA induces the release of primary granules and the production of oxygen radicals. ANCA also primes neutrophil and monocyte chemotaxis, signal trans-duction, and their potential to induce endothelial cell damage. These effects are enhanced by concurrent exposure to tumor necrosis factor (TNF). B cells may also play a role in pathogenesis as increased number of activated B cells in circulation correlates with disease activity.

III. PATHOLOGIC FEATURES

A. Lungs. Pulmonary involvement is characterized by parenchymal granulo-mas and necrosis (84%); granulomatous inflammation associated with a mixture of neutrophils, lymphocytes, plasma cells, histiocytes, and eosino-phils (59%); and capillaritis (33%).

B. Kidneys. Renal biopsies show focal and segmental glomerulonephritis in the majority of cases. Proliferative changes and fibrinoid necrosis may also be seen. Crescentic and sclerotic lesions may be seen in end-stage renal disease. Vasculitis and granulomas are very rare as is electron microscopy evidence of immune complex deposition.

IV. DIAGNOSTIC APPROACH

A. Diagnostic criteria. Diagnosis of Wegner's granulomatosis relies on the pathologic triad of necrosis, granulomas, and vasculitis. The granulomas are well formed and noncaseating, while the vasculitis involves medium-sized vessels. This diagnosis requires a large piece of tissue in

order to identify the complete triad. The availability of C-ANCA and Pr3-ANCA serology, with its high level of sensitivity (90%) and specificity (95%), provides an invaluable screening tool.

B. Tissue biopsies

1. **Lung biopsy.** Lung lesions are the sine qua non of both generalized and limited Wegener's granulomatosis. Open lung biopsies will be diagnostic in 90% of patients. Transbronchial biopsies, on the other hand, are only diagnostic 5% to 7% of the time.
2. **Renal biopsy.** Renal biopsy provides a less invasive procedure to diagnose generalized Wegener's granulomatosis. Although the focal glomeru-lonephritis itself is not pathognomonic, its presence in association with a positive C-ANCA serology and respiratory tract lesions is virtually diagnostic.
3. **Nasopharyngeal biopsy.** While upper respiratory complaints are the most common presenting symptom, the diagnostic combination of vas-culitis and necrosis and/or granulomatosis is found in <25% of nasopharyngeal biopsies. This is most likely caused by the limited amount of tissue available from these biopsy sites.

V. DIFFERENTIAL DIAGNOSIS

Wegener's granulomatosis must be differentiated from diseases exhibiting vasculitis, granulomas, glomerulonephritis, or a combination of these. Hyper-sensitivity angiitis, polymorphic reticulosis, lymphomatoid granulomato-sis, collagen vascular diseases, antiglomerular basement membrane disease (Goodpasture's syndrome), infectious granulomatous diseases, sarcoidosis, and neoplastic diseases are the most important considerations. The availability of screening C-ANCA serology has dramatically improved the ability to differentiate Wegener's granulomatosis from these processes; however, Wegener's granulomatosis must be differentiated from other ANCA-associated vasculiti-des including microscopic polyangiitis and CSS.

VI. TREATMENT

Therapy of WG has two components: induction of remission with initial immu-nosuppression and maintenance immunosuppressive therapy to prevent relapse.

A. Induction therapy

1. **Combined immunosuppression.** In generalized Wegener's granulomatosis, and probably also in most patients with limited Wegener's granulomatosis, a combination cyclophosphamide and corticosteroids is considered the standard treatment of choice.

   a. Cyclophosphamide. There are two cyclophosphamide dosing regimens, daily oral or monthly intravenous. Both have been shown to induce remission at similar rates, but the oral regimen has the advantage of a lower rate of relapse but the disadvantage of a higher total dose of cyclophosphamide, higher rate of infection, and more leu-kopenia. Daily maintenance therapy consists of cyclophosphamide 1.5 to 2 mg/kg/day oral or 0.5 to 1.0 g/m^2 body surface area/month intravenous (adjusted to keep absolute neutrophil count above 1,500/ mm^3). Cyclophosphamide should be continued for approximately 1 to 2 months after remission is achieved, which is typically 2 to 6 months. Considerable treatment related toxicities exist with cyclo-phosphamide—amenorrhea (57%), cystitis (50%), bladder cancer (5% to 6%), myelodysplasia (2%), and lymphoma (0.7%).

b. Corticosteroids. Three days of intravenous corticosteroids (e.g., methylprednisolone up to 7 to 15 mg/kg/day) may be indicated in select patients with fulminant disease. Otherwise, daily prednisone at 1 mg/kg should be continued for 1 month and then weaned to 20 mg daily by 2 months and weaned to off by 6 to 9 months, unless otherwise needed to control symptoms.

2. Alternative therapies

a. Rituximab. Rituximab, dosed as 375 mg/m^2/week for 4 weeks, may be an alternative to cyclophosphamide for newly diagnosed disease or for relapse following cyclophosphamide treatment. Early data from trials show rituximab is noninferior to cyclophosphamide in inducing remission among newly diagnosed patients and superior to cyclophos-phamide in those who failed initial treatment with cyclophosphamide. However, sufficient follow-up data are lacking; therefore, cyclophos-phamide is considered first-line therapy, and rituximab is considered alternative therapy for those who cannot tolerate cyclophosphamide.

b. Methotrexate. Earlier data suggested that methotrexate could be an alternative treatment for induction of remission in patients with non-organ- or nonlife-threatening disease. However, when compared with cyclophosphamide, time to induction is longer and relapse rates are higher with methotrexate. Given these findings, Methotrexate should be used in patients who do not tolerate cyclophosphamide or rituximab.

B. Maintenance therapy. Once remission is induced and induction therapy has concluded, maintenance therapy should be initiated. This typically required waiting for 1 to 3 days after last oral cyclophosphamide dose or 2 to 4 weeks after the last intravenous cyclophosphamide dose. Maintenance therapy then continues for 12 to 18 months after stable remission is achieved.

1. **Methotrexate.** Weekly oral methotrexate can be used for maintenance therapy after induction of remission. Initial doses are 0.3 mg/kg/week oral with an increase by 2.5 mg/week to a dose of 20 to 25 mg/week. Leucovorin should be given in combination with methotrexate. Methotrexate should be avoided in patients with severe renal impairment.
2. **Azathioprine.** The initiation of azathioprine 2 mg/kg/day oral can allow for the withdrawal of cyclophosphamide and the maintenance of remission. This may be the preferred maintenance therapy in patients with renal dysfunction.

C. Alternative therapies

1. **Trimethoprim–sulfamethoxazole (TMP/SMX).** TMP/SMX may be used for maintenance therapy. When dosed as one double-strength tab twice daily, it offers a lower relapse rate in those with upper respiratory disease. At minimum, TMP/SMX should be initiated at lower doses of one single-strength tab daily for *Pneumocystis (carinii) jiroveci* (PCP) pneumonia prophylaxis. Given its favorable side effect profile, TMP/SMX should be continued until immunosuppression ceases or is considerably minimized.

VII. PROGNOSIS

A. Untreated. The prognosis in untreated generalized Wegener's granuloma-tosis is extremely poor, with an average life expectancy of 5 months and a mortality rate of 93% at 2 years. The prognosis in limited Wegener's granulomatosis is somewhat better, and spontaneous remissions

have been reported, but death can occur rapidly due to progressive lung disease.

B. Treated. Combined induction immunotherapy induces remission in 85% to 90% of patients, with 75% of patients experiencing complete remission. Most remissions occur within 2 to 6 months. Despite this, 86% of patients experience morbidity related to their disease—hearing loss, nasal deformities, tracheal stenosis, and chronic kidney disease. Furthermore, profound immunosuppression results in increased rates of infection and malignancy.

SARCOIDOSIS

Sarcoidosis is a systemic granulomatous disease of unknown origin, involving multiple organs with variable frequency and intensity but invariably the lung. Pulmonary involvement manifests most commonly as isolated hilar lymphade-nopathy, parenchymal infiltrates, or both. Sarcoidosis has an overall incidence of 11/100,000 in the United States, but a much higher incidence in certain populations (e.g., African-Americans [40/100,000], Puerto Ricans [36/100,000], and Scandinavians [64/100,000]). Patients usually present in the third to fourth decade of life. Although there is no documented patient-to-patient transmission, sarcoidosis has occurred in families, suggesting a constitutional susceptibility or a common exogenous mechanism.

I. CLINICAL PRESENTATION

A. Symptoms and Signs

1. **General.** Approximately 80% of patients have symptoms at the time of diagnosis, the remainder being diagnosed from an incidental finding on chest x-ray. Constitutional symptoms (fever, weight loss, fatigue, malaise) develop insidiously in approximately one-third to one-half of patients. Patients presenting acutely with spiking fevers and erythema nodosum usually resolve most rapidly.
2. **Pulmonary.** Although over 90% of patients have pulmonary involvement, respiratory symptoms occur in 40% to 60% of patients and include shortness of breath, dry cough, substernal chest discomfort, and occasionally blood-streaked sputum. The physical findings are variable (depending on the stage) and nonspecific, consisting of tachypnea, crackles (diffuse or basilar), and sometimes wheezing (indicating endo-bronchial involvement).
3. **Extrapulmonary.** 50% to 80% of patients have granulomatous involvement of the liver, but <20% have hepatomegaly. Adenopathy, skin lesions, uveitis, peripheral nerve involvement, splenomegaly, arthritis, arrhythmias, salivary gland enlargement resulting in pain and/or dry mouth, nasal mucosal edema, and facial nerve palsy can be seen clinically, but most are more commonly diagnosed on biopsy or at autopsy. Clubbing is very rare. All patients suspected of having sarcoidosis should have a careful slit-lamp examination to rule out uveitis.

B. Laboratory findings. Serum angiotensin-converting enzyme (ACE) levels are elevated in 60% to 75% of all cases. However, mild elevations (up to two to three times normal) of ACE can be seen in multiple disease states. For this reason, ACE levels are not recommended for the work-up of sar-coidosis. The erythrocyte sedimentation rate is usually elevated in active disease. Leukopenia is common, while anemia is unusual. Polyclonal hyper-gammaglobulinemia is

present in 50% of cases. Hypercalcinuria with or without hypercalcemia may be present and appears to be due to secretion of 1,25-dihydroxy-vitamin D_3 by alveolar macrophages.

Cutaneous anergy may be present. The Kveim test is an intradermal injection of sarcoid spleen suspension that results in a typical noncaseating granuloma in 4 to 6 weeks in affected patients. The Kveim test is not commonly used because of a lack of a standardized, specific antigen and concern about transmission of infection.

C. Radiographic and nuclear medicine findings. There are five described x-ray stages of sarcoid. A normal chest x-ray (stage 0) occurs in 5% to 10% of patients on presentation. Bilateral hilar lymphadenopathy without infiltrates (stage I) is found in 35% to 45% of presenting patients. Linear and reticulonodular infiltrates with bilateral hilar lymphadenopathy (stage II) and parenchymal infiltrates alone (stage III) are each observed in 25% of patients on presentation. End-stage patients develop fibrosis, hilar retraction, bronchiectasis, and bullae formation, which are irreversible (stage IV). Rarely pneumothorax, unilateral pleural effusion, single or multiple cavities or nodules, or calcification of lymph nodes can be present. In 25% to 30% of cases, x-rays are not specific or atypical, and HRCT can be used to aid in diagnosis. Classic findings of sarcoidosis on HRCT include symmetric lymph node enlargement and small nodules tracking in the peribronchial vascular regions and adjacent to pleural surfaces, interlobular septa, and centrilobular areas. HRCT may also be useful in detecting early fibrosis not visible on x-rays. 18-FDG PET scanning may be helpful to identify occult lesions and reversible fibrosis; however, it is nonspecific. Newer PET scans with 18F-FMT (L-[3-18F]-methyltyrosine) are available and may be able to distinguish sarcoidosis from malignancy in 18-FDG PET–positive lesions. However, this modality is not yet widely available. Gallium scintigraphy detects pulmonary inflammation of any etiology and correlates poorly with disease activity, limiting its usefulness.

D. Physiologic tests. Pulmonary function tests commonly show a restrictive ventilatory defect with a decrease in vital capacity, total lung capacity, and diffusing capacity. If endobronchial sarcoidosis is present, an obstructive ventilatory defect may also occur.

II. IMMUNOLOGIC FEATURES

Sarcoidosis appears to be a cell-mediated (type IV) reaction, although the eliciting stimulus and etiology remain unknown. Pulmonary involvement is characterized by a lymphocytic infiltrate (alveolitis) of predominantly $CD4^+$ (helper/inducer) T cells. BAL often reveals $CD4^+$:$CD8^+$ T-cell ratios ranging from 2:1 up to 10:1 (normal: 1.2–1.6:1). Cutaneous anergy is common and may be due to sequestration of peripheral helper T cells ($CD4^+$) in the lung and at other granulomatous sites. These intrapulmonary T cells are activated as evidenced by their enhanced production of IL-2, gamma interferon, granu-locyte/macrophage colony–stimulating factor (GM-CSF), monocyte chemo-tactic factors, and soluble IL-2 receptors. Pulmonary macrophages are also activated with enhanced IL-1 and TNF secretion and enhanced antigen presenting capacity. Unfortunately, none of these immunologic markers or T-cell subsets sufficiently correlates with disease activity or prognosis to be clinically useful.

III. PATHOLOGIC FEATURES

The most characteristic pathologic feature of established sarcoidosis is the presence of well-formed, noncaseating granulomas composed of epithelioid and multinucleated giant cells surrounded by lymphocytes and monocytes. These are most commonly found in the alveolar septa, bronchial walls, and pulmonary vasculature. Asteroid or Schaumann bodies are frequently seen in giant cells. A peripheral inflammatory response is absent. Granulomas may convert to nonspecific hyaline scars or resolve completely over time. These findings occur in multiple organs and are observed throughout the lung interstitium and bronchial walls even when the chest x-ray appears normal.

IV. DIAGNOSTIC APPROACH

A. Criteria. The diagnosis requires three primary criteria:

1. A compatible clinical and radiographic presentation

2. Histologic evidence of a noncaseating granuloma from tissue biopsy

3. Careful exclusion of other disease processes, especially infectious diseases

B. Biopsy. Choice of biopsy site depends both on clinical presentation and ease or risk of obtaining tissue from a particular site. All biopsies should be stained and cultured to exclude mycobacterial and fungal infections.

1. **Lung.** Transbronchial biopsies, obtained through a fiberoptic broncho-scope, are the diagnostic modality of choice as four to six transbronchial biopsies yield a positive diagnosis in 85% to 90% of cases. Transbronchial biopsies are often positive even without clinical or radiologic evidence of pulmonary disease. Open lung biopsy is rarely necessary.
2. **Reticuloendothelial sites.** Palpable lymph nodes (80% yield), liver (70%, especially if alkaline phosphatase is elevated), and spleen (50%) are more invasive sites for biopsy and rarely performed. Mediastinoscopy is usually diagnostic in cases with mediastinal adenopathy and can be employed when transbronchial biopsies are nondiagnostic.
3. **Other sites.** Skin lesions, lacrimal and minor salivary glands, skeletal muscle, conjunctiva, and nasal mucosa all may yield positive biopsies with or without clinical involvement. Erythema nodosum should not be biopsied as its pathology will show panniculitis, and not granulomas, even if sarcoidosis exists.

V. DIFFERENTIAL DIAGNOSIS

Noncaseating granulomas are **nonspecific** and are seen in mycobacterial and fungal infections, lymphoma, foreign-body reactions, berylliosis, hypersen-sitivity pneumonitis, primary biliary cirrhosis, leprosy, brucellosis, tertiary syphilis, granulomatous arteritis, and lymph nodes draining malignant tumors. Radiographic mimics of sarcoid include lymphangitic carcinoma-tosis, berylliosis, coal worker's pneumoconiosis, and silicosis. Serum ACE levels are not specific and can be elevated in hyperthyroidism (81%), leprosy (53%), cirrhosis of the liver (28.5%), diabetes mellitus (24% to 32%), silicosis (21%), lymphoepithelioid T-cell lymphoma (Lennert's) lymphoma, and berylliosis. Ordinarily, neither mycobacterial nor fungal infections are associated with elevated levels of ACE, but exceptions have been reported. Sarcoidosis is a diagnosis of exclusion, and it is crucial to exclude these other diagnoses.

VI. TREATMENT

A. Indications. Sarcoidosis is associated with both a variable clinical course and a high spontaneous remission rate, making assessment of therapeutic regimens difficult. The decision to treat sarcoidosis is typically a function of the severity of symptoms, the degree of physiologic derangement, and the clinician's assessment of the likely natural history of the disease. When assessing patients for systemic immunosuppressive therapy, it is helpful to keep in mind the characteristics that lend to a more favorable course of disease: presence of bilateral hilar lymphadenopathy only, absence of symptoms, and European descent. It is reasonable to follow these patients with serial chest x-rays and pulmonary function tests at 6-month intervals. However, the following prognostic factors are unfavorable and may warrant systemic immunosuppression in order to alleviate symptoms or prevent the development of irreversible end-organ damage: age over 40 years old, extrapulmonary disease, multisystem involvement (three or more organs), worsening chest radiographs, and African descent.

B. Corticosteroids

1. **Local.** Acute iridocyclitis or uveitis responds well to topical corticosteroids (triamcinolone acetonide 1%). Skin lesions may respond to intralesional corticosteroid injections.
2. **Oral prednisone.** Although there are no controlled studies to support dosing regimens, prednisone at 20 to 40 mg/day in divided doses (1 to 2 mg/kg in children) is given for 3 to 6 months and then gradually tapered to 10 to 20 mg/day, if possible. Higher doses are used for cardiac and central nervous system disease. Therapy should continue for another 6 to 12 months with periodic attempts to further reduce the dosage or discontinue the drug. Alternate-day therapy (40 mg every other day) may also be an effective maintenance therapy and may be tapered by 10 mg every 3 months as tolerated. Lower doses and/or more rapid tapering may be possible in selected cases. Frequently, interruption or premature discontinuation of therapy results in relapse, which generally responds to increased doses of prednisone. Oral corticosteroids may or may not be effective in preventing fibrosis.
3. **Inhaled steroids.** ICSs have a limited role in the management of symptomatic pulmonary sarcoidosis. Budesonide has been well tested and demonstrates modestly improved lung function at the end of treatment with fewer relapses after 5 years. Studies of fluticasone have consistently shown it is not effective for sarcoidosis.

C. Alternative treatments. Several cytotoxic agents have been used to treat sarcoidosis and found to provide improvement including methotrexate, azathioprine leflunomide, antimalarial agents, and TNF antagonists.

1. **Chloroquine or hydroxychloroquine.** These medications have been best studied for cutaneous sarcoidosis and hypercalcemia. Chloroquine may also be used in pulmonary sarcoidosis as it improves lung function, symptoms, and radiographic abnormalities. Usual doses for chloroquine are 250 to 500 mg daily and for hydroxychoroquine 250 to 400 mg daily. Ocular toxicities are common, and regular eye exams are warranted.
2. **Methotrexate.** Methotrexate is widely used as a steroid-sparing agent. For sarcoidosis, the typical dose of MTX is 10 to 20 mg orally once a week. Serious toxicities of MTX

include hepatotoxicity, pneumonitis, and cytopenias. Folic acid supplementation can mitigate some of the risk of side effect from methotrexate. Liver function tests and complete blood counts must be monitored.

3. **Leflunomide.** Evidence in favor of using leflunomide in pulmonary sarcoidosis is limited. The typical dose is 20 mg/day. Leflunomide has been reported to cause hepatotoxicity, and periodic monitoring of liver function tests is advised.
4. **Azathioprine.** Data supporting the use of azathioprine in sarcoidosis are scant, but it is widely used as a second-line steroid-sparing agent. Dosing in the range of 50 to 200 mg/day should be titrated according to the patient's absolute neutrophil count. Complete blood count and liver function tests should be monitored.
5. **Infliximab.** Infliximab is proven to be effective for treatment of refractory pulmonary sarcoidosis. Patients with longer duration of disease or more severe impairment seem to benefit most from this medication. Dosing is 3 to 5 mg/kg IV every 4 to 8 weeks. Infliximab is generally well tolerated, but it does increase the risk for opportunistic infections, notably tuberculosis.

D. Monitoring of response. No single test is optimal for following the response to therapy. Overall clinical picture in conjunction with some combination of objective tests (pulmonary function tests, diffusing capacity, chest x-rays) relevant to the patients clinical situation is optimal. Lack of response may be present in inactive, fixed pulmonary fibrosis. Lung transplantation should be considered in patients with end-stage fibrosis.

VII. PROGNOSIS

Prognosis quoted in the literate depends heavily on the population studied. Overall mortality from sarcoidosis has been estimated to be 1% to 5%, and spontaneous remission occurs in one-third to two-thirds of patients within 5 years of diagnosis. Alternatively, sarcoidosis can persist with progressive granuloma formation occurring in 10% to 30% of patients, potentially leading to clinically significant organ impairment. Most patients will stabilize or improve with treatment. Relapse has been reported in up to 14% to 74% of patients when treatment is tapered or discontinued, and occurs more frequently in patients with treatment-induced remission than those with spontaneous remission.

IDIOPATHIC PULMONARY FIBROSIS

The term pulmonary fibrosis is commonly applied to a heterogeneous group of pulmonary disorders characterized by interstitial inflammation and thickening as well as varying degrees of parenchymal destruction and scarring. It is the common end pathway of many progressive interstitial lung diseases (ILDs). Over 160 different disease states have been associated with ILD and pulmonary fibrosis (see Table 10-2). Despite this long list, an underlying etiology is not identified in >50% of patients. These cases are referred to as idiopathic interstitial pneumonias (IIPs). IPF, also known as cryptogenic fibrosing alveolitis or by the histopathologic term usual interstitial pneumonitis (UIP), comprises one of the IIPs. Desquama-tive interstitial pneumonitis, respiratory bronchiolitis– associated ILD, nonspecific interstitial pneumonia (NSIP), acute interstitial pneumonia, bronchiolitis oblit-erans with organizing pneumonia, and lymphocytic interstitial pneumonia comprise the remainder of the IIPs and represent distinct clinical entities. The exact prevalence and incidence of IPF are unknown, but the

estimated prevalence is approximately 3 to 20/100,000 and the estimated incidence is approximately 7 to 10/100,000. Both the prevalence and incidence increase with age (average age of diagnosis is 66 years) and may reach as high as 175/100,000 for individuals over the age of 75. Men are more commonly affected than women. Familial cases do exist and follow an autosomal dominant pattern of transmission.

I. CLINICAL PRESENTATION

A. Symptoms and signs. The insidious and progressive development of shortness of breath, initially during exercise, and a nonproductive cough are the most common complaints (80% to100%) and often exist for more than 6 months before diagnosis. A small percentage of patients may present with abnormal chest x-rays without respiratory symptoms but invariably develop symptoms as the disease progresses. Up to 50% of patients develop systemic or constitutional symptoms (e.g., fatigue, weight loss, fever, myalgias, and arthralgias). Examination of the chest reveals late respiratory fine dry crackles ("Velcro" rales) at the bases. Late in the course of disease, clubbing of the fingers (25% to 50%) and evidence of cor pulmonale and pulmonary hypertension (accentuated P2, S3 gallop, right ventricular heave) are often found.

B. Laboratory findings. Hypergammaglobulinemia (80%), an elevated eryth-rocyte sedimentation rate (50%), positive rheumatoid factor (30%), positive antinuclear antibodies (15% to 20%), and circulating immune complexes are all relatively common with IPF but are nonspecific. Polycythemia rarely occurs even with hypoxemia.

C. Radiographic findings. The majority of patients with IPF will have an abnormal chest x-ray at presentation, although a normal film does not rule out disease. Typical findings on x-ray include bilateral, peripheral, reticular opacities, greatest in the lower lobes and associated with low lung volumes. Alveolar infiltrates are rare and should raise suspicion for another disease process. HRCT in IPF has a characteristic pattern of peripheral, subpleural, and basilar predominant reticulonodular opacities with occasional but minimal ground glass opacities, and with signs of architectural distortion such as honeycombing and traction bronchiectasis. In the appropriate clinical setting, radiographic findings may be sufficient to establish the diagnosis in >90% of cases and may remove the need for biopsy confirmation nearly 90% of the time. Furthermore, findings on HRCT can also be helpful in determining prognosis—higher fibrosis scores on chest HRCT are associated with increased risk of death.

D. Physiologic tests. Pulmonary function studies invariably reveal a restrictive ventilatory defect, with reduction in vital capacity, total lung capacity, and diffusing capacity. Patients with preexisting obstructive disease and hyperinflation from cigarette smoking may present with normal lung volumes. Occasionally, reduction in diffusing capacity may precede reduction in lung volume. Arterial blood gas analysis may be normal initially and later reveal hypoxemia initially with exercise and later at rest, as well as a respiratory alkalosis (hyperventilation) induced by stimulation of intrapulmonary stretch receptors. The hypoxemia at rest is secondary to ventilation/ perfusion mismatch, while the hypoxemia with exercise is due to the alveolar–arterial oxygen gradient increase from diffusion impairment and ventilation/perfusion mismatch.

II. IMMUNOLOGIC FEATURES

UIP histology is believed to arise from repeated epithelial injury resulting in the activation of airway epithelial cells (AECs), leading to fibroblast recruitment. Fibroblasts were thought to accumulate from the proliferation of resident fibroblasts. However, recent evidence has demonstrated tissue fibroblasts may also arise from both resident epithelial cells and bone marrow precursors (fibro-cytes): (1) Epithelial cells can take on mesenchymal characteristics in a process called epithelial–mesenchymal transition (EMT) during which primary type II alveolar endothelial cells and a type II–derived cell line undergo EMT in response to tissue growth factor (TGF-β1), with TNFα augmenting the frequency of this phenotypic transition. (2) Bone marrow–derived fibrocytes, cells that express mesenchymal markers such as collagen-1, are activated to form fibroblasts in the circulation and are recruited to the lung.

Once fibroblasts differentiate into myofibroblasts, they synthesize extracellular matrix by increasing the synthesis of collagen-1 and other extracellular matrix molecules. Because the integrity of the alveolar epithelium is severely disrupted in IPF lungs, and reepithelialization cannot proceed properly, myofibroblasts continue to accumulate and produce excessive amounts of extracellular matrix.

Ultimately, the development of fibrosis in IPF results from an imbalance of fibrogenic and antifibrogenic polypeptides. Key profibrotic agents, such as TGF-β1, insulin-like growth factor–binding protein-5, angiotensin II, and endothelin-1, are found to be overexpressed in IPF lungs. Similarly, antagonists to fibrosis, such as prostaglandin E2, are underexpressed.

III. PATHOLOGIC FEATURES

According to the International Consensus Statement published by the American Thoracic Society in 2010, UIP is the defining pathologic pattern of IPF. The hallmark of UIP is the temporal concurrence of normal lung alternating with interstitial inflammation, fibrosis, and honeycomb changes. These changes are most prominent in the subpleural and paraseptal areas. The interstitial inflammation is composed of alveolar septal infiltrates of lymphocytes and plasma cells as well as type 2 pneumocyte and bronchiolar epithelium hyperplasia. The areas of fibrosis have both dense collagen as well as areas of proliferating fibroblasts and myofibroblasts called "fibroblastic foci." The honeycombed zones consist of cystic fibrotic airspaces, which often are lined by bronchial epithelium and are filled with mucin. Smooth muscle metaplasia in the interstitium is commonly seen in areas of fibrosis and honeycomb change. Biopsies taken during an accelerated phase of illness (accelerated IPF) may show a combination of typical UIP findings along with a pattern of acute lung injury with diffuse alveolar damage.

IV. DIAGNOSTIC APPROACH

In 2010, several international pulmonary organizations adopted an international expert consensus statement in order to standardize diagnosis and treatment of IPF.

A. HRCT of the Chest. Thin section (≤2 mm) high-resolution reconstruction algorithm scans of the lungs obtained at full inspiration without respiratory motion are critical to the diagnostic algorithm. Expiratory or prone scans may also be helpful to exclude air trapping and remove obscuring dependent edema. If volumetric (spiral) images are obtained, coronal and sagital reconstruction helps to evaluate the distribution of reticulations.

HRCT CRITERIA FOR UIP PATTERN

1. Subpleural, basal predominance
2. Reticular abnormality
3. Honeycombing with or without traction bronchiectasis (possible UIP pattern if not present)
4. Absence of all of the following:
    a. Upper- or midlung predominance (suggestive of hypersensitivity pneumonitis)
    b. Perivascular predominance (suggestive of sarcoidosis)
    c. Extensive ground glass abnormality, exceeding reticular abnormality, (suggestive of NSIP)
    d. Profuse micronodules
    e. Discrete cysts, which may be multiple, bilateral, and/or removed from honeycombing (suggestive of LAM)
    f. Diffuse mosaic attenuation/air trapping (suggestive of RB-ILD, or HP)
    g. Consolidation in bronchopulmonary segments or lobes

B. Surgical lung biopsy. Transbronchial biopsy and BAL using a fiberoptic bron-choscope may be useful in excluding alternative diagnoses, especially sarcoidosis and infection. However, the small sample size of the biopsy is often insufficient to make an accurate diagnosis of IPF, and the cellularity observed on the BAL is a poor indicator of the interstitial inflammatory response. Bronchoscopy, therefore, rarely gives a definitive diagnosis of IPF or an accurate assessment of its level of activity. A definitive determination of the cause and activity state of diffuse interstitial fibrosis can only be made by examining tissue obtained by lung biopsy. Both thoracoscopic and open lung biopsy provide adequate tissue samples, and thoracoscopic biopsy is the preferred approach because of its lower morbidity and its association with a shorter hospital stay.

HISTOPATHOLOGIC CRITERIA FOR UIP PATTERN

1. Evidence of marked fibrosis/architectural distortion ±honeycombing in a predominantly subpleural/paraseptal distribution
2. Presence of patchy involvement or the lung parenchyma by fibrosis
3. Presence of fibroblastic foci
4. Absence of all of the following:
    a. Hyaline membranes (suggestive of diffuse alveolar damage/ARDS)
    b. Organizing pneumonia
    c. Granulomas
    d. Marked interstitial inflammatory cell infiltrate away from honeycombing
    e. Predominant airway centered changes
    f. Other features suggestive of an alternative diagnosis In *UIP Pattern***,** all criteria above are met.

Probable UIP pattern includes 1, 4, and either 2 or 3 above or honeycomb changes only.

Possible UIP pattern **i** ncludes 2 with or without interstitial inflammation, 4, and not fitting the UIP or probable UIP pattern.

V. DIFFERENTIAL DIAGNOSIS

IPF is a diagnosis of exclusion but can be diagnosed with a high degree of accuracy on clinical and radiographic grounds. The symptoms and radio-graphic or pathologic pattern of UIP seen in IPF can be seen in many disease states—collagen vascular diseases (e.g., rheumatoid arthritis, systemic sclerosis), familial diseases, asbestosis, and certain drug-induced lung diseases. However, the term IPF is generally reserved for the clinical scenario in which a UIP pattern on imaging or histology has no identifiable cause. Every effort should be made to identify treatable diseases such as tuberculosis and other infections, collagen vascular diseases, sarcoidosis, and the other IIPs including hypersensi-tivity pneumonitis and nonspecific interstitial pneumonitis.

VI. TREATMENT

Traditional therapies have attempted to reduce inflammation and reverse fibrosis. It is hypothesized that the disease may be more likely to respond to treatment in the earlier stages of the disease, before fibrosis has occurred. To date, no single therapy has been shown to clearly halt or reverse the sequelae of IPF or to improve quality of life. The Consensus Committee felt the preponderance of evidence to date suggests that **pharmacologic therapy is without definitive, proven benefit.** Long-term oxygen therapy and lung transplantation are strongly recommended in appropriate patients. For well-informed patients who strongly desire pharmacologic therapy, the following may be considered:

A. Combination therapy

1. **Corticosteroids**. Corticosteroids are used to minimize the progression of inflammation to fibrosis. When used in conjunction with azathio-prine, the typical starting dose of prednisone is 0.5 mg/kg/day (max. dose 100 mg/day). If the patient shows signs of improvement, the dose of prednisone is weaned by approximately 0.1 mg/kg/day to a low dose of 10 mg/day by 6 months.
2. **Azathioprine**. Azathioprine, when used in combination with cortico-steroids, may offer some improvement in DLCO and mortality, which may be clinically significant but is not statistically significant in clinic trials. Azathioprine is administered at 2 to 3 mg/kg/day to a maximum of 150 mg. Dosing should start at 25 to 50 mg/day and increase by 25 mg every 1 to 2 weeks until the target dose is achieved. The dose should be adjusted to keep the absolute neutrophil count >1,500, and periodic hepatocellular panels should be monitored. Prophylaxis for PCP should be given concurrently.
3. ***N*-acetylcysteine.** Oxidative lung injury is thought to be a contributor to lung injury in IPF. *N*-acetylcysteine (NAC) is a precursor to the anti-oxidant glutathione. NAC, when added to combination therapy with a corticosteroid and azathioprine, slowed the deterioration of vital capacity and diffusion capacity on PFTs compared with placebo. The usual dose of NAC is 1,800 mg/day divided in two to three doses daily.

B. *N*-acetylcysteine Alone

C. Anticoagulation. Unfractionated or low-molecular-weight heparin during hospitalization and warfarin during outpatient treatment may reduce mortality during hospitalization for acute exacerbations or disease progression.

D. Pirfenidone. Pirfenidone (5-methyl-1-phenyl-2-(1H)-pyridone) is an anti-fibrotic agent that works by inhibiting TGF-β–stimulated collagen synthesis, decreasing extracellular matrix, and blocking fibroblast proliferation. Pirfenidone may have a mild beneficial effect slowing the

decline in vital capacity on pulmonary function tests.

E. Treatment of pulmonary hypertension may be indicated for patients with severe pulmonary hypertension, but the choice of therapy is yet to be determined.

F. Treatment of asymptomatic gastroesophageal reflux may result in stabilization of pulmonary function and oxygen requirements.

G. Intermittent pulse therapy with intravenous methylprednisolone for acute exacerbations of IPF. Although supportive therapy is the mainstay of treatment for acute IPF exacerbations, intravenous methylprednisolone may be warranted in some cases. The dose, route of administration, and duration cannot be specified based upon current data; however, case series have reported 1 gm intravenously daily.

H. Strong recommendations have been made against interferon gamma 1b, bosentan, etanercept (recombinant TNF receptor), combined corticoste-roid therapy and immunomodulator without NAC, cyclosporine A, colchicine, and corticosteroid monotherapy.

I. Response to therapy. Only a small proportion of patients respond to conventional treatment.

1. **Predictors of mortality.** At baseline, predictors of mortality include level of dyspnea, DLCO < 40% reference, desaturation ≤ 88% during 6-minute walk, extent of honeycombing on HRCT, and pulmonary hypertension. Longitudinal predictors of mortality include increase in level of dyspnea, decrease in FVC by ≥10% absolute value, decrease in DLCO by ≥15% absolute value, and worsening of fibrosis on HRCT.
2. **Monitoring for progression of disease includes** respiratory symptoms (dyspnea), worsening of pulmonary functions tests (FVC, DLCO), progressive fibrosis on HRCT, or acute respiratory decline. Progression of disease is monitored over 4- to 6-month intervals. Patients who deteriorate and are eligible candidates should be referred for lung transplantation early on in their disease course.

VII. PROGNOSIS

The course of IPF is variable among individual patients. Rapid progressors, slow progressors, and stable patients are described in the literature. Any of these subtypes may develop acute worsening of their disease. The survival time after diagnosis is not well defined. Estimates of mortality 2 to 3 years after diagnosis listed in the literature may underestimate survival. Predictors of mortality include increased fibroblastic foci on biopsy and increased fibrosis scores on HRCT imaging. The most common causes of death are respiratory failure, cor pulmonale, infection, and lung carcinoma.

NONSPECIFIC INTERSTITIAL PNEUMONIA

NSIP originally referred to nonspecific histologic lesions in immunocompromised patients. In 1994, NSIP was redefined as a specific pattern that did not match criteria for other types of IIP. The pathogenesis of NSIP is still unclear but likely involves epithelial cell injury and involvement of fibroblast and myofibro-blasts. The prevalence of NSIP has been estimated at 1 to 9/100,000. The disease typically presents in the sixth decade of life. Idiopathic NSIP does not have a gender predilection, whereas NSIP associated with connective tissue disease has a predilection for women. Never-smokers also appear to be more affected.

I. CLINICAL PRESENTATION

A. Symptoms and signs. The clinical presentation of NSIP is breathlessness and cough of usually 6 to 7 months duration. Rales are present at the bases in the majority of patients. Fevers may be present in up to one-third of patients. The clinical characteristics of NSIP are insufficient to distinguish NSIP from other IIP.

B. Laboratory findings. BAL is likely to show a predominance of lymphocytes, which is more profound than that of UIP. However, BAL cell counts or differential alone cannot distinguish NSIP from UIP.

C. Radiographic findings. Chest radiographs typically show increased interstitial markings with basilar predominance. The predominant HRCT feature is ground glass opacification often associated with fibrosis seen as volume loss and reticular patterns with or without traction bronchiectasis. Honeycomb changes are rare. HRCT findings of idiopathic or CTD-associated NSIP are indistinguishable. Unlike UIP, HRCT findings alone are insufficient to make a diagnosis of NSIP, and a biopsy is required to confirm the diagnosis. Serial HRCTs in patients with NSIP vary greatly— some patients show improvement, whereas other patients exhibit signs of progression.

D. Physiologic tests. Pulmonary function tests exhibit a restrictive ventilatory defect with a reduction in DLCO.

II. IMMUNOLOGIC FEATURES

The understanding of the pathogenesis of NSIP is evolving. Epithelial injury and disregulated repair likely play a role in the pathogenesis of NSIP. Involvement of the immune system is also likely, given the presence of increased number of lymphocytes on BAL and dendritic cells on biopsy. Lastly, fibroblasts are a key effector in fibrotic lung disease. Fibroblasts in NSIP appear to behave more like normal fibroblasts than those in UIP.

III. PATHOLOGIC FEATURES

Although the histopathology of NSIP incorporates features of alveolar wall inflammation and fibrosis, the defining characteristic is its temporal homogeneity. The histopathologic pattern of NSIP can be divided into two categories: cellular NSIP and fibrotic NSIP. Cellular NSIP consists of mild to moderate chronic interstitial inflammation with little or no fibrosis. On the other hand, Fibrotic NSIP is characterized by interstitial thickening and uniform fibrosis of the same age with varying amounts of interstitial inflam-mation. The well-defined histopathologic pattern of NSIP differs from that of other IIPs, yet distinguishing NSIP from other IIPs remains difficult and disagreement between pathologists on the same biopsy exists. Furthermore, patterns of NSIP and UIP can exist within the same patient when biopsies are taken from multiple sites.

IV. DIAGNOSTIC APPROACH

The diagnosis of NSIP requires a combination of clinical, radiographic, and histopathologic findings.

A. Clinical presentation. A careful evaluation is necessary to distinguish idio-pathic NSIP from a

variety of conditions that exhibit NSIP histopathol-ogy such as connective tissue disease, hypersensitivity pneumonitis, drugs, infection, and immunosuppression.

B. Radiographic findings. Although findings on HRCT can suggest the diagnosis of NSIP, a confirmation surgical lung biopsy is necessary to make the diagnosis.

C. Pathologic features. Transbronchial biopsy is usually insufficient to make the diagnosis of NSIP. An open lung or video-assisted thoroscopy (VATS) biopsy is usually required. Evaluation of tissue specimens requires the careful exclusion of other forms of IIP.

V. DIFFERENTIAL DIAGNOSIS

The histopathologic pattern of NSIP can be found among a variety of other IIP and conditions such as connective tissue disease–associated ILD, hyper-sensitivity pneumonitis, drug-induced lung injury, infection, and immuno-suppression.

VI. TREATMENT

A minority of patients with mild disease may improve or stabilize without therapy. The remaining patients who have moderate to severe disease upon presentation, or who are progressing, should undergo treatment with immu-nosuppression.

A. Corticosteroids. The optimal dose and duration of glucocorticoids is unknown, but prednisone is typically initiated at 1 mg/kg/day oral (maximum dose of 60 mg/day), which is reduced to approximately 40 mg/day by 2 months and ultimately weaned off after 12 months of therapy. For patients who are severely symptomatic at presentation and require hospitalization, it is reasonable to use methylprednisolone at 15 to 30 mg/kg/day for 3 days before transitioning the oral prednisone regimen.

B. Other immunosuppressants. Patients with severe disease requiring prolonged courses of high-dose steroids, intolerance to glucocorticoids, or relapsing disease may benefit from additional immunosuppressant use.

1. **Azathioprine.** Azathioprine should be added to patients who meet the above criteria or who have responded to glucocorticoids but need a steroid-sparing agent. Azathioprine is usually started at 50 mg/day and increased by 25 mg/day every 2 weeks to a maximum dose of 1.5 to 2.0 mg/kg/day (maximum dose 200 mg/day). The most common toxic-ity is gastrointestinal upset, bone marrow suppression, and infection.
2. **Cyclophosphamide.** For patients who fail to respond to glucocorti-coids and azathioprine, cyclophosphamide may offer some benefit. The usual dose is 1.5 to 2 mg/kg/day oral (maximum dose 200 mg/ day). Cyclophosphamide can also be given monthly as 750 mg/m^2 of body surface area intravenously to minimize bladder toxicity. This dose should be reduced for patients over the age of 70 and those with renal dysfunction. The duration of cyclophosphamide therapy should depend on the response to therapy and associated toxicity, but an adequate trial of 3 to 6 months should be attempted and the medication should be discontinued after a 6- to 12-month course because of side effects.

C. PCP prophylaxis. While a patient is on prolonged high-dose steroid therapy or double immunosuppressive therapy, PCP prophylaxis with trimethoprim– sulfamethoxazole (or atovaquone with sulfa allergy) should be administered.

VII. PROGNOSIS

The overall prognosis is more favorable than that of UIP. Approximately two-thirds of patients are stable or improved after treatment, but mortality at 5 years after diagnosis is 20%. Patients with a cellular pattern on biopsy fare better than those with a fibrotic pattern. Initially, histopathology is a good predictor of mortality, but changes in physiology become more important over time.

CRYPTOGENIC ORGANIZING PNEUMONIA

Formerly known as idiopathic bronchiolitis obliterans organizing pneumonia, COP is the idiopathic form of organizing pneumonia. It is a distinct clinical entity with predominant features of pneumonitis rather than airway disease. Proliferation of granulation tissue and chronic inflammation are the hallmarks of this disease. The incidence and prevalence of the disease are unknown. It typically presents in the fifth or sixth decade of life and is distributed equally between men and women. Cigarette smoking is not a precipitating factor.

I. CLINICAL PRESENTATION

A. Symptoms and signs. The symptoms of COP often mimic that of community-acquired pneumonia. In a majority of cases, initial presentation is flu-like with fever, malaise, fatigue, and persistent, nonproductive cough. Dyspnea with exertion and weight loss are also seen. Physical exam reveals crackles, and wheezing while clubbing is rare. A normal physical exam can be seen in one-fourth of cases.

B. Laboratory findings. Routine laboratory tests are nonspecific. Lab abnormalities include leukocytosis (50%) and elevated ESR or CRP (70% to 80%). Autoantibodies are usually negative. BAL has a lower percentage of macro-phages but a higher percentage of lymphocytes, neutrophils, and eosinophils. The BAL CD4:CD8 ratio is also decreased due to the expansion of CD8 cells.

C. Radiographic findings. The most frequent radiographic finding of COP is multiple alveolar opacities, present bilaterally and peripherally, that are usually migratory. Their size varies from a few centimeters to a whole lobe, and the density can range from ground glass to consolidation. Air bronchograms are usually present in consolidated opacities. These chest radiograph manifestations of COP are quite distinctive, but other changes can include irregular linear or nodular opacities, pleural effusions, pleural thickening, hyperinflation, and cavities. Honeycombing is rarely seen at the time of presentation and, if present, occurs in only the few patients with progressive disease.

D. Physiologic tests. A mild to moderate restrictive ventilatory defect on pulmonary function test is common. Gas exchange abnormalities manifested as a reduced diffusion capacity are common. Mild hypoxemia is common, although severe hypoxia can occur.

II. IMMUNOLOGIC FEATURES

COP results from an immunologic response to inhaled antigens. However, the role of the pulmonary immune system in the pathogenesis of organizing pneumonia is still under

investigation. Several authors propose that COP may result from undetected viral infections, cryptic antigens, or capsid proteins. Reports of a "viral-type" prodrome for organizing pneumonia support this concept. After lung injury from exposure to an antigen occurs, the process of tissue repair begins. Granulation tissue plugs (Masson bodies) are required for reepi-thelialization and restoration of the basement membrane. The epithelial cells surrounding Masson bodies carry GM-CSF on their surfaces, which is thought to play a role in inflammatory recruitment thereby resolving.

III. PATHOLOGIC FEATURES

The characteristic histopathologic features are excessive proliferation of granulation tissue within small airways and alveolar ducts and chronic inflammation in the surrounding alveoli. Intraluminal buds of granulation tissue consist of fibro-blasts and myofibroblasts that extend from one alveolus to the next through the pores of Kohn, giving a characteristic "butterfly" pattern. Additional key features are temporal uniformity and a patchy and peribronchiolar distribution. Foamy macrophages are common, but giant cells are not. Honeycombing is rare.

IV. DIAGNOSTIC APPROACH

The diagnosis of COP relies on characteristic radiographic or pathologic features of the disease in the appropriate clinical setting, and in the absence of features suggestive of another process. Empiric therapy can be initiated in individuals with a compatible HRCT and clinical symptoms.

A. Clinical presentation. In a majority of cases, patient will present with flulike symptoms with nonproductive cough and dyspnea for approximately 2 months duration. Patients classically have had a prior misdiagnosis of an acute, infectious pneumonia and have not clinically responded to trials of antibiotics.

B. Radiographic findings. HRCT features of COP are pathognomonic and allow for a radiographic diagnosis in the hands of an experienced clinician. Atypical radiographic presentations require lung biopsy.

C. Lung biopsy. Transbronchial biopsy is recommended as the first-line diagnostic approach since the finding of characteristic intra-alveolar buds on histopathologic examination is sufficient to make a provision diagnosis of organizing pneumonia. However, it must be noted that the small tissue sample size obtained from a transbronchial biopsy and crush artifact occurring from tissue handling can make the exclusion of other histopathologic processes difficult. If needed, lung biopsy via VATS is generally well tolerated and allows for large tissue sample size from multiple lobes.

V. DIFFERENTIAL DIAGNOSIS

Any disease process that causes organizing pneumonia must be considered including poorly resolving bacterial and other infectious pneumonias, NSIP of rheumatologic (dermatomyositis–polymyositis) or other cause, Wegener's granulomatosis, chronic eosinophilic pneumonia, hypersensitivity pneumonia, postobstructive pneumonia, abscesses, aspiration pneumonia, organizing acute respiratory distress syndrome/diffuse alveolar damage, radiation injury, drug-associated lung injury, and malignancy. On imaging, COP can resemble chronic eosinophilic pneumonia, low-grade pulmonary lymphoma, and bron-choalveolar carcinoma.

VI. TREATMENT

Spontaneous resolution is rare, and the mainstay of treatment is glucocorti-coids, although resection incidental to a VATS biopsy is adequate initial therapy in focal disease. Prednisone is usually given at 0.75 to 1 mg/kg/day orally for 4 to 8 weeks, until the patient shows signs of improvement. In severe, rapidly progressive cases, methylprednisolone 15 to 30 mg/kg/day intravenously in divided dose for three days can be used. Thereafter, steroids can be weaned off in 3 to 6 months if the patient remains stable to improved. As this disease can recur, patients should be monitored closely, and glucocorticoid therapy should be increased or resumed at the first signs of recurrence.

VII. PROGNOSIS

Complete clinical and physiologic improvement occurs in two-thirds of treated patients. Approximately one-third of patients have persistent disease despite treatment. Improvement with treatment is dramatic and occurs within 1 to 2 weeks of initiation of steroids. Recurrence is common once steroids are withdrawn, but this does not appear to affect overall long-term prognosis.

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11

Atopic Dermatitis and Contact Dermatitis

Mark Boguniewicz, Marcella Aquino, and Luz Fonacier

ATOPIC DERMATITIS

Atopic dermatitis (AD) is a chronic, relapsing, highly pruritic, inflammatory skin disease that frequently precedes the development of asthma and/or allergic rhinitis. It is the most common chronic skin disease of young children but can affect patients of any age. The associated sleep disruption, school absenteeism, occupational disability, and emotional stress can have a signircant impact on the quality of life of patients and their families. AD may also be associated with significant morbidity, especially when complicated by erythroderma or concomitant infection. The prevalence of AD has continued to increase, affecting more than 10% of children at some point during childhood in most countries. Because wide variations in prevalence both within and between countries inhabited by similar ethnic groups have been documented, environmental factors may be critical in determining disease expression.

I. CLINICAL ASPECTS

A. Natural history. AD typically presents in early childhood with onset before 5 years of age in approximately 90% of patients. Although most children will have milder disease over time, they may continue to have persistent or frequently relapsing dermatitis as adults. Patients with mutations in the gene encoding filaggrin (*FLG*) protein (see Immunopathologic Aspects below) are more likely to have persistent AD.

B. Clinical features. AD has no pathognomonic skin lesion(s) or unique laboratory parameters. Diagnosis is based on the presence of major and associated clinical features (Table 11-1). The principal features include **pruritus**, a chronically relapsing course, typical morphology and distribution of the skin lesions, and a history of atopic disease. The presence of pruritus is critical to the diagnosis of AD, and patients with AD have been shown to have a reduced threshold for pruritus.

Table 11-1 Clinical Features of Atopic Dermatitis

(Adapted from Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Dermatol Venereol* (Stockh) 1980;92:44–47.)

1. **Acute atopic dermatitis** is characterized by intensely pruritic, erythem-atous papules associated with excoriations, vesiculations, and serous exudate.
2. **Subacute atopic dermatitis** is characterized by erythematous, excoriated, scaling papules.
3. **Chronic atopic dermatitis** is characterized by thickened skin with accentuated markings (lichenification) and fibrotic papules. Patients typically have dry skin. Significant differences can be observed between the pH, capacitance, and transepidermal water loss of AD lesions compared with uninvolved skin in the same patients and with the skin of normal controls.
4. During **infancy**, AD involves primarily the face, scalp, and extensor surfaces of the extremities, although infants can have flexural involvement and the diaper area is typically spared. When involved, it may be secondarily infected with *Candida*, in which case, the dermatitis does not spare the inguinal folds. In contrast, infragluteal involvement is a common distribution in children.
5. In **older patients** with long-standing disease, the flexural folds of the extremities are the predominant location of lesions. Localization of AD to the eyelids may be an isolated manifestation but should be differentiated from an allergic contact dermatitis (ACD) (as discussed in Allergic Contact Dermatitis). Chronic rubbing of the skin can result in prurigo nodules.

C. Complicating features

1. **Infections.** Patients with AD have increased susceptibility to infection or colonization with a variety of microbial organisms.

   a. Viral infections include *Herpes simplex* (HSV) and molluscum contagiosum. Patients can have generalized dissemination of HSV termed eczema herpeticum or Kaposi varicelliform eruption. Corneal involvement is a serious complication and may constitute a medical emergency. A **polymerase chain reaction** (PCR) for viral identification and culture of fluid from freshly unroofed vesicle can be helpful, especially as HSV lesions can become secondarily impetiginized with the viral component undiagnosed. It is worth remembering that molluscum is a contagious disease, and although it often resolves spontaneously, it can spread and school-aged

children need to be treated or their lesions need to be covered.

b. Fungal infections can also cause AD to flare. *Malassezia sympodialis* is a lipophilic yeast, and IgE antibodies against *M. sympodialis* have been found predominantly in patients with head and neck dermatitis. The potential importance of *M. sympodialis* as well as other dermatophyte infections is further supported by the reduction in clinical severity of AD in patients treated with antifungal agents in some studies. Occasionally, resistant cheilitis or fissures may respond to antifungal therapy.

c. Bacterial infections, particularly *Staphylococcus aureus*, are frequent in patients with AD. *S. aureus* can be cultured from more than 90% of AD skin lesions. In contrast, only 5% of healthy subjects harbor this organism. *S. aureus* proteases contribute to skin barrier abnormalities. Methicillin-resistant *S. aureus* (MRSA) has become an increasingly important pathogen in patients with AD. Although recurrent staphylococcal pustulosis can be a significant problem in AD, invasive *S. aureus* infections are rare and should raise the possibility of an immunodeficiency such as hyper-IgE syndrome.

2. **Hand dermatitis.** Patients with AD often have nonspecific hand dermatitis. This is frequently irritant in nature and aggravated by repeated wetting, especially in the occupational setting.
3. **Ocular problems.** Ocular complications associated with AD can lead to significant morbidity. Atopic keratoconjunctivitis is always bilateral, and symptoms include itching, burning, tearing, and copious mucoid discharge. It is frequently associated with eyelid dermatitis and chronic blepharitis and may result in visual impairment from corneal scarring. Keratoconus is a conical deformity of the cornea that may result from persistent rubbing of the eyes in patients with AD and allergic rhinitis. Anterior subcapsular cataracts may develop during adolescence or early adult life.
4. **Psychological issues.** Patients with AD may have high levels of anxiety and problems dealing with anger and hostility, which can exacerbate the illness. Stress or frustration can precipitate an itch–scratch cycle. In some cases, scratching is associated with secondary gain or with a strong component of habit. In addition, severe disease can have a significant impact on patients' self-esteem and social interactions.

D. Differential diagnosis. A number of diseases may be confused with AD (Table 11-2). While patients with hyper-IgE syndrome have eczematous rash and high IgE levels, systemic infections especially staphylococcal or fungal lung disease distinguish them from AD patients. Patients with immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome are males who typically present in infancy with intractable diarrhea. Distribution in the genital and axillary areas, presence of linear lesions, and skin scrapings help to distinguish scabies from AD. While contact dermatitis can be confused with AD, it can also complicate AD especially in patients whose AD appears to flare with therapy (see Contact Dermatitis below). It is especially important to recognize that in an adult with eczematous dermatitis and no history of childhood eczema or atopic features, cutaneous T-cell lymphoma needs to be ruled out. Biopsies should be obtained from three separate sites since histology may be similar to AD.

Table 11-2 Differential Diagnosis of Atopic Dermatitis

Congenital disorders
Netherton's syndrome
Metabolic disorders
Zinc deficiency
Pyridoxine (vitamin B_6) and niacin deficiency
Multiple carboxylase deficiency
Phenylketonuria
Immunodeficiencies
Wiskott-Aldrich syndrome
Severe combined immunodeficiency
Hyper-IgE syndrome
IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome
Chronic dermatoses
Seborrheic dermatitis
Contact dermatitis
Nummular eczema
Lichen simplex chronicus
Infections and infestations
Scabies
HIV-associated dermatitis
Malignancies
Cutaneous T-cell lymphoma (mycosis fungoides/Sézary's syndrome)
Proliferative disorders
Letterer-Siwe disease

IgE, immunoglobulin E; HIV, human immunodeficiency virus

II. IMMUNOPATHOLOGIC ASPECTS

A. Epidermal barrier and genetics. Patients with AD have an abnormal skin barrier with increased transepidermal water loss. A number of genes important for maintaining barrier homeostasis are encoded in the epidermal differentiation complex on chromosome 1q21. Filaggrin protein is involved not only in epidermal barrier integrity but also in epidermal hydration and pH through its amino acid breakdown products that contribute to natural moisturizing factor. Mutations in the gene encoding filaggrin (*FLG*) have been found in approximately 50% of patients with moderate to severe AD and are the strongest risk factors for AD. Patients with *FLG* mutations have early-onset, severe, and persistent AD and are at greater risk for allergic sensitization and asthma. Buccal swabs or blood can be sent for identification of common *FLG* mutations (e.g., Advanced Diagnostic Laboratories, National Jewish Health, Denver, CO).

B. Immunohistology. Skin biopsies are rarely needed but may be useful if the diagnosis is in question or the patient does not respond to therapy as expected.

1. **Uninvolved skin** in AD patients is not normal which has therapeutic implications (see Proactive/Maintenance therapy below). Uninvolved skin is colonized by *S. aureus* and has increased transepidermal water loss and immune cell abnormalities.
2. **Acute lesions** are characterized by intercellular edema of the epidermis (spongiosis) and intracellular edema. A sparse lymphocytic infiltrate may be observed in the epidermis, whereas a marked perivenular infiltrate consisting of lymphocytes, some monocytes, and rare eosinophils, basophils, and neutrophils is seen in the dermis. Mast cells are found in normal numbers in different stages of degranulation.
3. **Chronic lesions** often demonstrate prominent hyperkeratosis of the epidermis with increased numbers of epidermal Langerhans' cells and predominantly monocytes/macrophages in the dermal infiltrate. Mast cells are increased in number but

are not degranulated. Lymphocytes, in both acute and chronic lesions, are predominantly CD3, CD4, and CD45RO memory T cells that also express CD25 and human leukocyte antigen DR (HLA-DR) indicative of intralesional activation. In addition, almost all of the infiltrating T cells express high levels of the skin homing receptor, cutaneous lymphocyte antigen (CLA), which is a ligand for the vascular adhesion molecule, E-selectin. Langerhans' cells found in the epidermis and dermis of chronic lesions are potent activators of autologous resting CD4 T cells and have been shown to express high affinity receptors for IgE. The latter appears to play an important role in cutaneous allergen presentation to Th2-type cells. Activated eosinophils are present in significantly greater numbers in chronic as compared to acute lesions. In addition, deposition of eosinophil major basic protein (MBP) can be detected throughout the upper dermis and to a lesser extent deeper in the dermis, especially in involved areas. MBP may contribute to the pathogenesis of AD through its cytotoxic properties and its capacity to induce basophil and mast cell degranulation.

C. Immunoregulatory abnormalities. Immunoregulatory abnormalities during acute AD include an increase in interleukin 4 (IL-4) expression, whereas chronic disease is primarily associated with IL-5 expression. IL-13 expression is also higher in acute lesions, whereas chronic lesions are characterized by increased IL-12 (a potent inducer of interferon γ [IFN-γ] synthesis) and IFN-γ (a Th1-type cytokine) expression. IL-16, a chemoattractant for $CD4^+$ T cells, is more highly expressed in acute than in chronic skin lesions. In addition, the C-C chemokines, regulated upon activation, normal T cell expressed and secreted (RANTES), monocyte chemotactic protein 4, and eotaxin are also increased in atopic lesions and likely contribute to the chemotaxis of eosinophils and Th2-type lymphocytes into the skin. Cutaneous T cell–attracting chemokine may play an important role in the preferential attraction of CLA^+ T cells into the skin. IL-31 has been recognized as an important CLA^+ T cell–derived pruritogenic cytokine, and serum IL-31 levels have been shown to correlate with disease activity in AD. Chronic colonization and superinfection by *S. aureus* can contribute to pruritus and inflammatory changes in AD since *S. aureus*–derived toxins rapidly induce IL-31 in the skin of AD patients. Keratinocyte-derived thymic stromal lymphopoietin, a key regulator for allergic inflammation, is overly expressed in the skin of AD patients and exerts effects on a number of key cells including T cells, mast cells, basophils, and eosinophils leading to a Th2-polarized milieu.

III. IMMUNOLOGIC TRIGGERS

A. Foods. Double-blinded, placebo-controlled food challenges (DBPCFC) have demonstrated that food allergens can cause AD exacerbations in a subset of patients, primarily young children. Approximately one-third of children with chronic moderate to severe AD may have associated IgE-mediated food hypersensitivity. Seven foods (milk, egg, peanut, soy, wheat, fish, and tree nuts) account for nearly 90% of the positive DBPCFC. These data reaffirm the need to consider the role of food allergens in children with AD who do not respond readily to conventional therapy. Notably, elimination of proven food allergens results in amelioration of skin disease and a decrease in spontaneous basophil histamine release.

B. Aeroallergens. The evidence supporting a role for aeroallergens in AD includes the finding of

both allergen-specific IgE antibodies and allergen-specific T cells. Exacerbation of AD can occur with exposure to allergens such as house dust mites. Direct contact with inhalant allergens can also result in eczematous skin eruptions. Dust mite proteases contribute to skin barrier breakdown. Environmental control measures have resulted in clinical improvement of AD.

C. Microbes. AD patients are frequently colonized by *S. aureus* that produce toxins with superantigenic properties, causing significant activation of pro-inflammatory cells and cytokines. In addition, patients make specific IgE antibodies directed against the staphylococcal toxins found on their skin. *S. aureus*–specific IgE has been shown to correlate with clinical severity of AD and may contribute to persistent inflammation or exacerbations of AD.

IV. TREATMENT

A. Conventional therapy

1. **Education.** Education of patients and their families is an essential component of successful management of a chronic illness such as AD. Adequate time and teaching materials are necessary to provide effective education, because most patients or parents will forget or confuse the skin care recommendations given to them without written instructions. A written step-care treatment plan will lead to improved outcomes, and this should be reviewed and adjusted at follow-up visits. Educational information can be obtained from the National Eczema Association (800-818-7546 or www.nationaleczema.org) and the Lung Line (800-222-LUNG or www.njc.org). An instructional DVD for skin care is available from the Professional Education Department at National Jewish Health (Denver, Colorado). Patients and caregivers should be counseled regarding the natural history of the disease and prognosis with appropriate vocational counseling.
2. **Identification and elimination of exacerbating factors**
   - **a. Irritants.** Patients with AD have a lowered threshold of irritant responsiveness and need to avoid irritants including detergents, soaps, and chemicals. Cleansers with minimal defatting activity and a neutral pH should be used rather than soaps, especially after exposure to chlorine ("sensitive skin" products are usually well tolerated). Air temperatures at home and work should be temperate to minimize sweating. In addition, nonsensitizing sunscreens should be used to prevent sunburn.
   - **b. Allergens.** Avoidance of foods confirmed by controlled challenges results in clinical improvement. The *in vitro* ImmunoCAP assay has been shown to measure specific IgE to egg, milk, peanut, and fish allergens with clinically relevant predictive values (see chapter on Food Allergy). In dust mite allergic individuals, environmental control measures aimed at reducing dust mite allergen loads (e.g., use of dust mite–proof covers for pillows and mattresses and washing sheets in hot water) have been shown to improve AD in patients allergic to dust mite allergen.
3. **Hydration.** Skin of AD patients shows enhanced transepidermal water loss from both involved and uninvolved skin consistent with impaired barrier function. Bathing helps restore epidermal water content, may remove allergens, and may reduce colonization by *S. aureus*, and the associated relaxation can be therapeutic. Bathing or soaking affected areas should be done for approximately 10 to 15 minutes in warm water. A wet washcloth or

towel can be applied to facial or neck eczema. Isolated hand or foot dermatitis can be treated with soaks in basins. Baths may need to be taken on a long-term daily basis and may even need to be increased to several times daily during flares of AD. Showers may be appropriate for patients with milder disease. Addition of substances such as oatmeal to the bath water may be soothing to patients but does not promote skin hydration. Bath oils do not effectively add moisture to the skin and can make the tub dangerously slippery. After hydrating the skin, patients should be instructed to gently pat away excess water with a soft towel and immediately apply topical medication or moisturizer (as discussed below). Because wet skin is more permeable to water, it is essential that the skin be covered within the first few minutes to prevent evaporation. Appropriate use of hydration and topicals should help heal and maintain the skin barrier.

4. **Moisturizers.** Use of moisturizers, especially when combined with hydration therapy, will help restore and preserve the stratum corneum barrier. Moisturizers may also decrease the need for topical cortico-steroids. Moisturizers are available in lotions, oils, creams, and ointments. In general, ointments have the fewest additives and are the most occlusive, although in a hot, humid environment, their use may lead to trapping of sweat with associated irritation of the skin. Lotions and creams may be irritating because of added preservatives or fragrances. Lotions contain more water than creams and may have a drying effect due to evaporation. Oils are also less effective moisturizers. Moisturizers should be obtained in the largest size available because they typically need to be applied several times each day on a chronic basis. Shortening (e.g., Crisco) can be used as an inexpensive moisturizer. Petroleum jelly (e.g., Vaseline) is not a moisturizer but can be used as a sealer after hydrating the skin. Several topical prescription creams (e.g., Atopiclair, Eletone, EpiCeram, MimyX) are not FDA-regulated products but are registered as medical devices. They have no age or length of use restrictions and are indicated for pruritic dermatoses.

5. **Corticosteroids**

    a. General. Topical corticosteroids have been the mainstay of treatment for AD. They reduce inflammation and pruritus and are effective for both the acute and chronic phases of the disease. They impact multiple resident and infiltrating cells primarily through suppression of inflammatory genes. Topical corticosteroids are available in potencies ranging from extremely low (group 7) to high (group 1) (Table 11-3). Products approved for younger patients include desonide 0.05%, alclometasone, and fluticasone 0.05% cream and lotion, although only for up to 21 to 28 consecutive days.

Table 11-3 Representative Topical Corticosteroid Preparations

Group 1 (super potent)
- Clobetasol propionate (Temovate) 0.05% ointment/cream
- Betamethasone dipropionate (Diprolene, Diprosone) 0.05% ointment/cream
- Halobetasol propionate (Ultravate) 0.05% ointment/cream
- Diflorasone diacetate (Fluorone, Psorcon) ointment 0.05%

Group 2 (potent)
- Mometasone furoate (Elocon) 0.1% ointment
- Halcinonide (Halog) 0.1% cream
- Fluocinonide (Lidex) 0.05% ointment/cream
- Desoximetasone (Topicort) 0.25% ointment/cream
- Amcinonide (Cyclocort) 0.1% ointment

Group 3 (potent)
- Fluticasone propionate (Cutivate) 0.005% ointment
- Halcinonide (Halog) 0.1% ointment
- Betamethasone valerate (Valisone) 0.1% ointment
- Amcinonide (Cyclocort) 0.1% cream, lotion
- Triamcinolone acetonide (Aristocort) 0.5% cream

Group 4 (mid-strength)
- Mometasone furoate (Elocon) 0.1% cream
- Triamcinolone acetonide (Kenalog) 0.1% ointment/cream
- Fluocinolone acetonide (Synalar) 0.025% ointment
- Fluticasone propionate (Cutivate) 0.05% cream, lotion
- Betamethasone valerate (Valisone) 0.01% lotion

Group 5 (mid-strength)
- Fluocinolone acetonide (Synalar) 0.025% cream
- Hydrocortisone valerate (Westcort) 0.2% ointment
- Triamcinolone acetonide (Kenalog) 0.1% lotion

Group 6 (mild)
- Desonide (DesOwen) 0.05% ointment/cream/lotion
- Alclometasone diproprionate (Aclovate) 0.05% ointment/cream
- Fluocinolone acetonide (Synalar) 0.1% cream

Group 7 (least potent)
- Hydrocortisone (Hytone) 2.5% & 1% ointment/cream
- Dexamethasone (Decadron) 0.1% cream

b. Choosing the appropriate compound. Use of a particular drug should depend on the severity and distribution of the skin lesions. Patients should be informed of the strength of topical corticosteroid they are given and the potential side effects. Patients often make the mistake of assuming that the potency of their prescribed corticoste-roid is based solely on the percent noted after the compound name (e.g., believing that hydrocortisone 2.5% is more potent than beta-methasone dipropionate 0.05%) and may apply the preparations incorrectly. In general, the lowest potency corticosteroid that is effective should be used, although using a topical corticosteroid that is too low in potency may result in persistence or worsening of AD. In such cases, a step-care approach with a mid- or high-potency preparation (although usually not to eczema of the face, axillae, or groin) followed by a low-potency preparation may be more successful. Often, patients are only prescribed a high-potency corticosteroid and told to discontinue use after a period of time, which can result in rebound flaring of the AD, similar to what is often seen with oral corticosteroid therapy. Occasionally, therapy-resistant lesions may respond to a potent topical corticosteroid under occlusion, although this approach should be used with caution and reserved primarily for eczema of the hands or feet.

c. Choosing the appropriate vehicle. The vehicle that the product is formulated in can alter the potency of the steroid and move it up or down in this classification. Generic formulations of topical steroids are required to have the same active ingredient and the same concentration as the original product. However, many generic products do not have the same vehicle formulation and their bioequivalence can vary

significantly. In general, the same steroid will be most potent in an ointment base, followed by emollient, gel, cream, and lotion. Topical steroids are available in a variety of bases including ointments, creams, lotions, solutions, gels, sprays, foam, oil, and even steroid-impregnated tape (Table 11-3). There is, therefore, no need for a pharmacist or patient to compound these medications, especially as compounding adds considerably to cost of therapy. Ointments are most occlusive, have the fewest additives, provide better delivery of the medication, and decrease evaporative losses. During periods of excessive heat or humidity, creams may be better tolerated than ointments because the increased occlusion may cause itching or follicu-litis. In general, however, creams and lotions, while easier to apply, may be less effective and can contribute to xerosis. Solutions can be used on the scalp or other hirsute areas, although the alcohol in them can be quite irritating when used on inflamed or excoriated lesions. Ingredients used to formulate the different bases may be irritating to individual patients and may cause sensitization.

d. Other practical considerations. Inadequate prescription size often contributes to poor compliance and a suboptimal outcome, especially in patients with generalized disease. In addition, dispensing the prescribed medication in larger (1 lb) quantities when available can result in significant cost savings for the patient. It is worth remembering that approximately 30 g of medication is needed to cover the entire body of an average adult. The fingertip unit (FTU), defined as the amount of topical medication that extends from the tip to the first joint on the palmar aspect of the index finger, has been proposed as a measure for applying topical corticosteroids. It takes approximately 1 FTU to cover the hand or groin, 2 FTUs for the face or foot, 3 FTUs for an arm, 6 FTUs for the leg, and 14 FTUs for the trunk.

e. Patients or caregivers should be instructed to avoid placing a moisturizer either under or over topical steroid, as this will reduce the effectiveness of the steroid. **Side effects** of topical corticosteroids are infrequent with low- to medium-potency topical corticosteroids when used appropriately, even when applied for extended periods of time. More potent topical steroids cause thinning of the skin most commonly. Several weeks of topical corticosteroid application can lead to a decrease in collagen and elastin synthesis and subsequent skin fragility, dermal atrophy, striae, telangiectasia, purpura, and poor wound healing. In addition, hypopigmentation, secondary infections, and acneiform eruptions may occur. Local side effects are most likely to occur on the face and on the intertriginous areas, and therefore only low-potency corticosteroids should be used in these areas on a routine basis. Perioral dermatitis may also occur with the chronic use of topical corticosteroids on the face and is characterized by erythema, scaling, and follicular papules and pustules that occur around the mouth, alar creases, and sometimes on the upper lateral eyelids. ACD to corticosteroids is discussed in the Contact Dermatitis section under Specific Allergens, Topical Medications below.

Systemic side effects are extremely rare with topical corticosteroids. However, prolonged use of high-potency compounds especially under occlusion may cause systemic side effects and should therefore be used judiciously.

f. Oral corticosteroids. The use of oral corticosteroids should be avoided in a chronic disease such as AD. Although patients may experience rapid and dramatic relief with oral corticosteroids, this is all too often followed by rebound flaring of the dermatitis. Short courses of prednisone or prednisolone are occasionally used with the introduction of other treatment measures. Gradual tapering of the oral corticosteroid and intensification of topical skin care may decrease the occurrence of rebound exacerbations that can occur with systemic corticosteroid use.

6. **Topical calcineurin inhibitors.** Since their approval by the FDA in 2000 and 2001, respectively, tacrolimus ointment (protopic 0.03% and 0.1%) and pimecrolimus cream (Elidel 1%) have become well-established, effective, and safe nonsteroidal treatments for AD. They are currently indicated as second-line treatment for intermittent, noncon-tinuous use in children aged 2 years and older with moderate to severe AD (tacrolimus ointment 0.03%) and mild to moderate AD (pimecrolimus cream 1%). Tacrolimus ointment 0.1% is indicated for patients 16 years and older. Patients, caregivers, and even health care providers frequently misunderstand their place in the treatment algorithm and have concerns about the boxed warning for these drugs. A Joint Task Force of the American College of Allergy, Asthma, and Immunology and the American Academy of Allergy, Asthma, and Immunology reviewed the available data and concluded that the risk–benefit ratios of tacrolimus ointment and pimecrolimus cream are similar to those of most conventional therapies for the treatment of chronic relapsing eczema. A case– control study of a large database found no increased risk of lymphoma with the use of TCIs. Common side effects include burning or stinging (usually transient) at the site of application.
7. **Proactive (maintenance) therapy**. In patients whose eczema can be brought under control but tends to relapse in the same locations, topical anti-inflammatory therapy can be instituted on normal appearing (but not immunologically normal) skin, rather than waiting for eczema to flare in a traditional reactive approach. Studies with topical corticosteroids and a topical calcineurin inhibitor (tacrolimus ointment) have shown clinical benefit with this approach. It is important to recognize that eczema first needs to be brought under control before a two to three times weekly long-term regimen can be instituted.
8. **Tar preparations.** Although the anti-inflammatory properties of tars are not as pronounced as those of topical corticosteroids, they may be useful in reducing the need for topical corticosteroids in chronic maintenance therapy of AD. Tars are used primarily in shampoos for scalp inflammation (e.g., T/Gel) or as bath additives (e.g., Balnetar). Tar preparations should not be used on acutely inflamed skin, as this may cause irritation. Side effects include inflammation of hair follicles and photosensitivity.
9. **Anti-infective therapy.** Treatment should ideally be based on results of culture and sensitivities in the case of bacterial infection, PCR or culture for viral infection, and scrapings or culture for suspected fungal infection.

a. Antibacterial therapy. Systemic antibiotics may be necessary to treat AD secondarily infected with *S. aureus*. First- (e.g., cephalexin) or second-generation (e.g., cefuroxime axetil) cephalosporins given for 7 to 10 days are usually effective (e.g., cephalexin 500 mg twice daily or 25 to 50 mg/kg divided twice daily for

pediatric patients). Erythromycin-resistant organisms are common, which limits the usefulness of macrolides. Clindamycin and trimethoprim/sulfamethoxazole remain effective for most strains of community-acquired MRSA. Long-term maintenance antibiotic therapy should be avoided to decrease colonization or infection by resistant organisms. Topical antibiotics such as mupirocin (Bactroban) applied three times daily to affected areas for 7 to 10 days or (Altabax) retapamulin ointment 1% (Altabax) twice daily for 5 days can be used for limited areas of secondarily infected dermatitis. Topical neomycin use can lead to ACD as neomycin is a common allergen (see under Contact Dermatitis below). Treatment for nasal carriage with intranasal mupirocin twice daily for 5 to 7 days may lead to clinical improvement of AD. Patients and caregivers need to be educated that the best defense against microbes is an intact skin barrier, and basic skin-care principles as above need to be emphasized. In addition, topical anti-inflammatory therapy with corticosteroids or calcineurin inhibitors can reduce *S. aureus* colonization. Although antibacterial cleansers have been shown to be effective in reducing bacterial skin flora, they can be irritating to the skin of AD patients. One controlled study in children with AD showed that dilute bleach baths (one-half cup 6% sodium hypochlorite in 40 gallons water) twice weekly for 3 months with nasal mupirocin twice daily 5 days/month resulted in improved clinical scores, although patients remained colonized by *S. aureus*.

b. Antiviral therapy. Patients with disseminated eczema herpeticum usually require treatment with systemic acyclovir or valacyclovir. Recurrent cutaneous herpetic infections can be suppressed with prophylactic oral antiviral. Treatment options for molluscum contagiosum include cryotherapy, cantharidin, topical antiviral (e.g., imiquimod), or curettage.

c. Antifungal therapy. Superficial dermatophytosis and *M. sympodialis* can be treated with topical or systemic antifungal drugs. A subset of patients with AD may respond to a course of empiric treatment with antifungal agents.

10. **Antihistamines.** Pruritus is the cardinal symptom of AD and even partial reduction can result in significant improvement in quality of life for patients with severe disease. In general, antihistamines do not have a large effect on pruritus associated with AD. First-generation antihistamines appear to be most useful because of their tranquilizing effects and can be dosed primarily in the evening to lessen daytime drowsiness. In patients with very severe pruritus and sleep disruption, doxepin which has both histamine H1- and H2-receptor binding affinity and a long half-life may be given as a single 10- to 50-mg dose in the evening. Use of topical antihistamines and local anesthetics should be avoided because of potential sensitization.
11. **Sedative-hypnotics.** If sleep disruption caused by nocturnal pruritus remains severe, medications such as zolpidem (Ambien) or eszopiclone (Lunesta) given at bedtime may be appropriate for short-term use.
12. **Psychosocial/behavioral interventions.** Counseling, relaxation, behavioral modification, or biofeedback may be of benefit, especially in patients with habitual scratching.

B. Recalcitrant disease

1. **Wet wraps.** Wet dressings can be used together with hydration and topical therapy in

severe AD or to potentiate therapy with less potent topical corticosteroids. The prolonged hydration and occlusion provided by these wraps increases the absorption of topical medications and promotes healing. They can also serve as an effective barrier against the persistent scratching that often undermines therapy. Total body dressings can be achieved by using wet pajamas or long underwear with dry pajamas or sweatsuit on top. Hands and feet can be covered by wet tube socks under dry tube socks. Alternatively, the face, trunk, or extremities can be covered by wet gauze with dry gauze over it and secured in place with an elastic bandage or by pieces of tube socks. Dressings may be removed when they dry out or they may be rewetted. Wet wraps are often best tolerated and most convenient at bedtime. Overuse of wet dressings can result in chilling, maceration of the skin, or secondary infection.

2. **Hospitalization.** AD patients who are erythrodermic or who appear toxic may require hospitalization. This may also be appropriate for patients with severe generalized disease resistant to therapy. Removing the patient from environmental allergens or stressors, together with intense education and assurance of compliance with therapy, results in marked clinical improvement in many cases. The patient can also undergo appropriately controlled provocative challenges to help identify potential triggers while in the hospital.
3. **Phototherapy.** Ultraviolet (UV) light therapy under the supervision of a dermatologist (not tanning beds!) can be a useful treatment modality for chronic recalcitrant AD. Patients who do not experience photoex-acerbations of their AD and who are not fair complexioned may be good candidates, although access to treatment, time involved, and cost need to be considered. Photochemotherapy with oral methoxypsoralen therapy followed by UVA (PUVA) may be indicated for patients with severe disease, especially with failure of topical therapy or in patients with significant corticosteroid side effects. Short-term adverse effects may include erythema, pruritus, and pigmentation, whereas long-term adverse effects include premature skin aging and cutaneous malignancies. Topical PUVA has no risk of systemic side effects and may be useful for chronic hand eczema resistant to other treatment.
4. **Cyclosporin A.** Patients with severe refractory AD may respond to oral cyclosporin A (CsA) (3 to 5 mg/kg/day) with often rapid resolution of pruritus, more gradual healing of eczematous lesions and improved quality of life. Side effects including nausea, abdominal discomfort, paresthesias, hypertension, hyperbilirubinemia, and renal impairment with increased serum urea and creatinine require appropriate monitoring. CsA is indicated for up to 12 months, and the potential for progressive or irreversible nephrotoxicity with extended treatment needs to be weighed against the clinical benefit of this treatment.
5. **Mycofenolate mofetil (CellCept)**. Limited data in adults and children with AD show benefit and infrequent, though potentially serious adverse effects. Treatment for AD would be off-label.

C. Experimental and unproven therapies

Limited data on benefit of subcutaneous allergen desensitization in adult AD patients with house dust mite allergy and sublingual desensitization in children with AD sensitized to house dust mite have been reported. Intravenous immunoglobulin and omalizumab have shown efficacy in small numbers of patients but not in controlled studies. Specific markers have not been found to identify

potential responders. A Cochrane review concluded that probiotics are not an effective treatment for eczema in children and that probiotic treatment carries a small risk of adverse events.

CONTACT DERMATITIS

Contact dermatitis (CD) represents a spectrum of inflammatory skin reactions induced by exposure to external substances and manifests as erythematous, vesicular, papular, or lichenified pruritic skin lesions. CD is a common skin problem, resulting in nearly 8 million physician visits per year. It is estimated that there are more than 85,000 chemicals that may be encountered in the world environment; the majority of these agents will induce an irritant CD, and approximately 2,800 of these substances may act as contact allergens. Identifying and avoidance of the allergen is essential for the appropriate management of patients with CD. When avoidance is not achieved, the condition may become chronic and disabling and may lead to a major impairment in quality of life. Although CD can affect patients of all ages, the exact prevalence of CD in the general population is unknown due to the fact that most patch test (PT) studies have been performed in selected groups rather than in the general population. In one cohort study that included questionnaire, interview, exam, and patch testing, the point prevalence of contact allergy was 15.2%.

I. TYPES OF CONTACT DERMATITIS AND PATHOGENESIS

A. Irritant contact dermatitis (ICD) is the most common type of reaction to a contactant and is caused by nonspecific direct tissue activation. T cells are stimulated to release inflammatory cytokines such as tumor necrosis factor-a, IL-1, IL-8, and GM-CSF via nonspecific immune mechanisms. ICD is a syndrome that results from contact with agents that may chemically abrade, physically irritate, or damage the skin. Irritation is produced by a wide variety of external agents including water, soap, detergents, acids/bases, and bodily fluids (urine, saliva, and stool) and by environmental factors such as washing, overhydration, improper drying, perspiration, and temperature extremes (Table 11-4). The inflammatory response to irritants appears to be both dose- and time-dependent. Any impairment to the epidermal barrier layer (e.g., fissuring, overhydration,) renders the skin more susceptible to an irritant effect. The clinical presentation of ICD is usually restricted to the skin site directly in contact with the offending agents, with little or no extension beyond the site of contact. ICD may precede the development of allergic CD.

Table 11-4 Important Cutaneous Irritants

Soaps, detergents
Janitorial cleaning agents
Disinfectants
Solvents, degreasers
Oils, greases
Plastic resins
Paints, inks, varnishes
Glues, adhesives
Gasoline, diesel, jet fuels
Metalworking fluids
Dust, dirt, sewage
Cement, mortar, plaster
Fiberglass
Acids, alkalis
Fruits, vegetables
Grasses, weeds, shrubs
Shampoos
Permanent wave solutions
Pesticides, herbicides, fungicides
Fertilizers

B. Allergic contact dermatitis (ACD) represents an immunologic, antigen-induced reaction mediated via type IV cell-mediated hypersensi-tivity; allergens conjugate with proteins in the skin to induce epidermal keratinocytes to release inflammatory cytokines. Langerhans' cells process peptides from these allergens in conjunction with HLA class I molecules and present to naive T cells. Once activated, T cells cause effector cells to release proinflammatory cytokines that lead to intense perivascular inflammation. Following this period of sensitization, subsequent cutaneous exposure to the same antigen results in movement of these antigen-specific Th1 cells from regional lymph nodes to the systemic circulation and then to the affected area of skin. Within 12 to 36 hours, release of mediators from these Th1 cells causes a delayed-type inflammatory skin reaction. Further exposures to the same antigen result in progressive shortening of the period required for development of the skin reaction. The thickness and integrity of the skin also strongly influences the process of sensiti-zation, thinner sites (i.e., eyelids, earlobes, and genital skin) being most vulnerable, whereas thicker skin (i.e., palms of hands and soles of feet) are more resistant.

C. Photocontact dermatitis (PCD) is a form of CD which is caused by either irritants or allergens in combination with the effects of light (Table 11-5). PCD may be either phototoxic or photoallergic in nature. Mechanisms resemble those in ICD or ACD except that activation of an UV light-absorbing chemical substance on the skin surface must occur before a toxic reaction in tissues or a hapten–protein conjugate can be formed.

Table 11-5 Important Photocontact Irritants and Allergens

- Coal tar
  - Crude coal tar
  - Pitch
  - Creosote
- Dyes
  - Acridine
  - Eosin
  - Fluorescein
  - *Rhodamine*
  - Rose Bengal
- Plants
  - *Umbelliferae*
    - Celery
    - Carrots
    - Bergamot
    - Dill
    - Cow parsley
    - Parsnip
    - Fennel
    - Giant hogweed
    - Angelica
  - *Rutaceae*
    - Limes
    - Lemons
    - Gas plant
    - Rue
    - Bitter orange
  - *Moraceae*
    - Figs
  - *Compositae*
    - Yarrow
    - Mayweed
- Miscellaneous
  - Buttercup
  - Mustard
  - Agrimony
  - Goose foot
  - Scurfy pea
  - St. John's wart
- Oils and fragrances
  - Angelica root oil
  - Bergamot oil
  - Lemon oil
  - Lime oil
  - Bitter orange oil
  - Rue oil
  - Cedarwood oil
  - Sandalwood oil
  - Lavender oil
  - Musk ambrette
  - 6-Methylcoumarin
- Drugs
  - Chlorothiazides
  - Phenothiazines
  - Nonsteroidal anti-inflammatory drugs
  - Tetracyclines
  - Sulfonamides
  - Griseofulvin
- Sunscreens
  - p-Aminobenzoic acid, esters
  - Benzophenones
- Antimicrobials
  - Halogenated salicylanilides
  - Bithionol
  - Hexachlorophene
  - Dichlorophen

II. DIAGNOSIS OF CONTACT DERMATITIS

A. History

Elements of history to be obtained from patients include agents used, evolution of lesions, body areas involved, and time course from contact with allergen to emergence of lesions if known. Ascertaining causative allergens from history alone proves to be more difficult in chronic cases of CD. Previous treatment and response to such treatment should be elicited in the history. Worsening of the dermatitis after initiation of treatment should lead to suspicion of CD to topical medications (antibiotics, corticosteroids, or other skin products). Occupational history should focus on the nature of the work, potential allergens and irritants to which the patient is in contact with, the length of exposure, and mitigating factors such as hand washing. CD is the second most common cause of work-related compensation cases; thus this aspect of history is essential to investigate. Material safety data (MSD) sheets are available for every product used in the workplace and should be reviewed in all cases involving work-related dermatitis. Leisure activities and hobbies such as gardening, painting, carpentry, and

photography may also be important in the etiology of CD. Lastly, concomitant medical problems may be a contributing factor (other atopic diseases, skin barrier defects). The impaired epidermal barrier layer in AD patients subjects them to a greater risk for irritation and/or allergic sensitization.

B. Physical examination

Objective physical exam findings include the identification of all of the primary and secondary skin lesions any of which may be secondarily affected by crusting and/or excoriations. The body's exposed areas, especially the hands and face, are most frequently involved with airborne related contact dermatitis. CD can be described as acute, subacute, or chronic. Acute dermatitis can present with erythematous papules, vesicles, and even bullae. Chronic CD is generally pruritic and erythematous and may be associated with crusting, scaling, fissuring, excoriations, and lichenification. Subacute is a mixture of these features.

1. Specific body sites

a. Hands. Hand dermatitis deserves special consideration not only because it is extremely common (10% of women and 4.5% of men) but also because the differential diagnosis can be challenging. The increasing prevalence of hand involvement with increasing age is probably due to increased water exposure and occupational insults, along with coexisting irritant dermatitis. Because the palmar skin is much thicker than the dorsum of the hands, ACD is rarely noted on the palms and presents most often as vesicles on the thinner skin of the fingertips, nail folds, and the dorsum of the hands. Involvement of the dorsal hand and finger combined with volar wrist suggests AD as contributing etiologic factor. ICD commonly presents as a localized dermatitis without vesicles in webs of fingers; it extends onto the dorsal and ventral surfaces in an "apron" pattern and includes the dorsum of the hands, palms, and ball of the thumb.

b. Eyelids. Eyelids are particularly sensitive because the skin is thin in nature, and substances applied to the scalp or face or on the fingers easily come in contact with the eyelids. Airborne pollen and dust usually cause such powerful palpebral reactions that absence of eyelid involvement makes the diagnosis based on airborne pollen and dust unlikely. ACD occur roughly in one-half to two-thirds of patients with eyelid dermatitis. Other less common causes of eyelid dermatitis (in order of decreasing frequency) include ICD, AD, and seborrheic dermatitis. If bilateral upper and lower eyelids are involved, there is a greater risk of ACD as the cause of the dermatitis. Contact allergens that commonly cause eyelid dermatitis include fragrance in cosmetics, even those applied to other areas of the body (i.e., nails, scalp), nickel, preservatives, gold, rubber, and shampoos.

c. Face. Similar to eyelid dermatitis, facial dermatitis can result from allergens transferred to the face from other regions of the body. ACD to moisturizers, sunscreens, foundations, and powders produces a symmetrical dermatitis. Rubber-sensitive individuals may react to rubber sponges, masks, and/or balloons that come into contact with the face. A spouse's fragrance and cosmetics may produce a unique, unilateral facial eruption. The scalp skin is relatively resistant to allergens in shampoos and hair dyes, and the dermatitis may instead be manifest on the face or eyelids.

d. Mucous membranes. Although oral and/or mucus membrane contact reactions are rare, contact sensitivity has been described as a factor in recurrent oral ulcerations. Objectively, changes may be barely visible, or may vary from a mild erythema to a fiery red color, with or without edema. Dental- and mouth-care products contain abrasives and a number of sensitizing chemicals. Cinnamon flavorings and peppermint are probably the most common causes of allergic stomatitis from dentifrices and chewing gum. In patients with contact allergy to orthodontics, nickel is the most common allergen although other responsible metals include mercury, chromate, gold, cobalt, beryllium, and palladium. Among these metals, mercury (used in amalgam) has most often been implicated but rarely proven as a cause of oral allergic reactions.

e. Generalized, scattered dermatitis. Dermatitis with a generalized distribution is a difficult diagnostic challenge because it lacks the characteristic distribution that gives a clue as to the possible diagnosis of ACD. The two most common allergens that have been identified in this type of dermatitis are nickel and balsam of Peru; however, other positive PT reactions include preservatives, propylene glycol, and textile dyes.

f. Systemic allergic contact dermatitis is a localized or generalized inflammatory skin disease that occurs in sensitized individuals when they are exposed to the allergen either orally, transcutaneously, intravenously, or by inhalation (Table 11-6). Patients allergic to ethylene-diamine may react to systemic aminophylline and antihistamines of the piperazine or ethanolamine families. Similar reactions have been reported to glucocorticoids, diphenhydramine, neomycin, penicillin, sulfonamides, thiuram, colophony, balsam of Peru, and fragrance mix (reaction to spices such as cloves, nutmeg, cinnamon, cayenne pepper). Nickel-sensitive patients may develop systemic reactions from the ingestion of nickel in tap water or foods cooked in nickel utensils and from eating canned foods and food with high nickel content.

Table 11-6 Important Contact Allergens

Topical sensitizer	Source of Systemic Reaction
Ethylenediamine	Intravenous aminophylline Oral piperazine/ethanolamine antihistamines
Diphenhydramine	Oral, parenteral diphenhydramine
Sulfonamides, benzocaine	Oral para-amino sulfonamide–containing hypoglycemic agents (tolbutamide, chlorpropamide)
Corticosteroids	Oral, parenteral, intra-articular corticosteroids
Nickel	Nickel in tap water, foods cooked in nickel utensils, canned foods, foods with high nickel content

C. Patch testing

The PT remains the gold standard for differentiating ACD from other forms of dermatitis and for diagnosing the cause of ACD. Antigen selection and test interpretation require experience and expertise on the part of the clinician. The most common contact allergens are listed in Table 11-7.

Table 11-7 Important Contact Allergens

- Plants
  - *Rhus*
    - Poison ivy
    - Poison oak
    - Poison sumac
  - *Compositae*
    - Chrysanthemums
    - Ragweed
    - Liverwort
    - Feverfew
  - *Primula*
    - *Primula obconica*
  - Tulips
    - Tulip bulbs
  - *Lichens*
    - *Frullania*
  - Woods
    - Rosewood
    - Pine
    - Cocobolo
- Metals
  - Nickel
  - Chromate
  - Cobalt
  - Gold
  - Mercury
- Rubber chemicals
  - Thiurams
  - Mercapto compounds
  - Carbamates
  - PPD antioxidants
- Plastic resins
  - Epoxies
  - Acrylics
  - Phenolics
  - Formaldehyde resins
  - Hardeners, curing agents
- Organic dyes
  - p-Phenylenediamine
  - Color developers
  - Textile dyes
- Blocide preservatives
  - Formaldehyde
  - Quaternium-15
  - Imidazolidinyl urea
  - Chloroisothiazolinone
  - p-Chloro-m-xylenol
  - Parabens
- Topical medications
  - Neomycin
  - Bacitracin
  - Thimerosal
  - Benzocaine
  - Corticosteroids
- Miscellaneous
  - Fragrances
  - Colophony (rosin)
  - Ethylenediamine di-HC

1. **Who to patch test.** The greater the level of suspicion for ACD, the more frequently the correct diagnosis will be made. Therefore, a thorough history eliciting potential environmental sensitizers plays a key role in diagnosis. The majority of patients are allergic to a single allergen or a single group of allergens. PT is warranted for any patient with a chronic, pruritic, or recurrently eczematous or lichenified dermatitis. The usefulness of PT is enhanced with the number of allergens tested, and allergens not commercially available frequently give relevant reactions. In addition, personal products are a useful supplement especially in facial or periorbital dermatitis.

2. How to patch test. PTs should be applied to the upper back, ideally free of eczematous lesions or other skin lesions including but not limited to CD, AD, psoriasis, tinea corporosis, or pityriasis. The upper back should also be free of hair (hair should be removed from back 1 to 2 days prior to placement of patch) and emollients to ensure good adherence of patch. An FDA-approved standardized test kit is available as the T.R.U.E. Test (Thin Layer Rapid Use Epicutaneous Test). Other kits are also available including the North American Contact Dermatitis Series (which includes around 70 allergens based on relevant antigens from the North American Contact Dermatitis Group), European standard series, international standard series, Japanese standard series, etc. Sources of these allergens include AllergEAZE

(www.allergEAZE.com), Trolab, Hermal, and Dormer (www.dormer.com). The T.R.U.E. test contains 28 standardized antigens and a negative control (Table 11-8). Kits for specific exposures (hairdressers, bakers, shoes, plants, photo allergens, dental, textiles, metals, medicaments, sunscreens, and corticosteroids) are also available. The testing materials are suspended on a chamber (finn or allergEAZE PT chambers) which is attached to an adhesive backing and then applied to the patient's back. Personal products that are used as is can be placed on the chamber and applied to the back. Personal products that are washed off (shampoo, conditioner, and body or facial washes) need to be diluted prior to placement (1:10 to 1:1,000 dilution). Liquids are applied to paper disks on top of the PT chambers (Table 11-9).

Table 11-8 T.R.U.E. Test Panel of Standard Antigens

Substance	Source
Nickel sulfate	Metal objects
Wool alcohols (lanolin)	Ointments, creams, lotions, soaps
Neomycin sulfate	Antibiotic creams, lotions, ointments
Potassium dichromate	Cement, industrial chemicals
Caine mix (benzocaine, tetracaine hydrochloride, dibucaine hydrochloride)	Topical anesthetic medications
Fragrance mix	Toiletries, perfumes, flavorings
Colophony	Adhesives, sealants, pine oil cleaners
Paraben mix	Cosmetics, skin creams, paste bandages
Negative Control	
Balsam of Peru	Resin used in cosmetics, perfumes, flavoring agent in cough syrups, lozenges, chewing gum, and candles
Ethylenediamine dihydrochloride	Stabilizer, emulsifier, and preservative in topical fungicides, topical antibiotics, eye drops, and nose drops
Cobalt dichloride	Metal-plated objects and costume jewelry
p-tert-Butylphenol formaldehyde resin	Waterproof glues, leather goods
Epoxy resin	Adhesives, surface coatings, paints
Carba mix	Stabilizer in rubber products, pesticides, glues
Black rubber mix	Antioxidant and antiozonate in almost all black rubber products (e.g., tires, hoses)
Cl + Me–isothiazolinone	Antibacterial preservative in shampoos, creams, lotions, and other skin care products
Quaternium-15	Preservative in shampoos, lotions, soaps, and other skin care products
Mercaptobenzothiazole	Vulcanization accelerator used in most rubber products and some adhesives
p-Phenylenediamine	Permanent and semipermanent hair dyes
Formaldehyde	Building materials and plastics industry
Mercapto mix	Accelerators found in rubber products
Thimerosal	Mercury-containing preservative in cosmetics, nose drops, and eardrops
Thiuram	Antimicrobials and antioxidants found in rubber products
Diazolidinyl urea	Formaldehyde releasing preservative in skin, hair, and cosmetic products
Imidazolidinyl urea	Formaldehyde releasing preservative in skin, hair, and cosmetic products
Budesonide	Topical corticosteroid
Tixocortol-21-Pivalate	Topical corticosteroid
Quinoline mix	Medicament

T.R.U.E. Test, thin-layer rapid use epicutaneous test.

Table 11-9 Patch Testing to Nonstandard Antigens

Agent	Test Concentration
"Leave-on" products	As is
"Wash-off" products	1:10–1:100 dilution
Household products	1:100–1:1,000 dilution
Clothing, gloves, plants	As is
Industrial products	With great caution

Products obtained from the workplace should be tested with great caution. The employer should have an MSD sheet for each agent used in the workplace, and it should be reviewed for toxicity, including effects upon the skin. When tested, toxic agents must be diluted similarly to the agents listed above. It is prudent not to use allergens that are not labeled or are of unknown origin to reduce toxic reactions.

3. **Reading the patch test.** PT should be removed 48 hours after placement, with an initial reading at this time, and again 72 to 96 hours after placement. PT results should be evaluated 30 minutes after removal of the test materials to allow for the irritative effect from the adhesive material to subside. The reading at 72 to 96 hours is considered most clinically relevant since about one-third of relevant allergens negative at the 48-hour reading become positive in 72 to 96 hours. Also, irritant reactions tend to disappear by 96 hours. The standardized grading system should be used at both the 48 and 72- to 96-hour reading (Table 11-10).

Table 11-10 Grading and Interpreting Patch Test Results

PT grading
0 = no reaction
+/– = mild erythema only
1+ = 50% of PT site erythematous with edema
2+ = 50% of PT site with papular erythema
3+ = 50% of PT site with vesicles or bulla
Clinical interpretation of grading
0 = no evidence of contact allergy
+/– = doubtful existence of contact allergy
1+ = possible (or false-positive) contact allergy
2+ = probable contact allergy
3+ = definite contact allergy

Certain allergens can present with positive results beyond 5 days and include metals (gold, potassium dichromate, nickel, and cobalt), topical antibiotics (neomycin, bacitracin), topical corticosteroids, and *p*-phenylenediamine (PPD). However there are other allergens, which dissipate after 5 days and include balsam of Peru, benzoic acid, disperse Blue #124, fragrance mix, methylydibromo glutaronitrile/phenoxyethanol, and octyl gallate.

The current T.R.U.E. test has a higher false negative rate to neomycin, thiuram mix, balsam of Peru, fragrance mix, cobalt, and lanolin. T.R.U.E. test is also lacking antigens which were listed in the top thirty most positive allergens on the North American Contact Dermatitis Group 2003-2004 panel including bacitracin, methyldibromo glutaronitrile, 2-bromo-2-nitropropane-1,3-diol, cinnamic aldehyde, propylene glycol, dimethylol dimethyl (DMDM) hydantoin, iodopropynyl butylcarbamate, ethylene urea/melamine formaldehyde, disperse blue, and amidoamine.

Once positive results on PT have been obtained, it is important to determine the relevance to the patient's current dermatitis. A positive response would be definite if the result of a "use test" with

suspected item was positive or the reaction of PT with the object or product was positive. A probable response can be considered if the suspected allergen is verified in known skin contactants with a consistent clinical presentation. A possible response can be considered when the patient's skin is in contact with materials that likely contain the suspected allergen. Past relevance is when the patient no longer has the exposure to the PT-positive allergen. Thus the clinician has to understand the sources of antigen in the patient's environment. Positive reactions may be relevant to current or previous dermatitis.

Multiple true-positives can occur and common combinations include nickel sulfate/PPD/benzocaine (PPD and benzocaine cross sensitize); thiuram mix/carba mix/mercapto mix (all in rubber); form-aldehyde/quaternium-15 (quaternium-15 is a formaldehyde releaser); paraben/quarternium-15/formaldehyde (preservatives frequently combined and cosensitize); cobalt/nickel (cobalt used in alloys with nickel and chromium); and cobalt/potassium dichromate. Mild responses may still represent allergic reaction and the patient may need to be retested.

4. **Factors that affect patch test results.** Oral corticosteroids (prednisone, 20 mg/day or more) can suppress or diminish PT results; high-potency topical corticosteroids will also significantly reduce PT reactions and should be discontinued from the PT site 7 days prior to testing. If possible, oral corticosteroid should be discontinued or reduced to <20 mg/day or PT deferred until after corticosteroid has been discontinued. There is limited data for patients on oral cyclosporin. A recent study on patients on systemic immunosuppression and cytokine inhibitors showed that patients on medications including cyclosporine, azathioprine, infliximab, adalimumab, etanercept, methotrexate, mycophenolate mofetil, and tacrolimus can still have positive PT reactions, and those who continue to have significant PT (at least ++) positivity had good response with the avoidance of the positive PT allergen. Systemic and topical H1-antihistamines do not need to be stopped prior to or during PT.
5. **Photopatch testing** involves performing PT with the addition of light and represents the gold standard for the diagnosis of PCD. It is a complex procedure and should be performed in specialized centers due to the requirement of appropriate light sources, antigens, and light opaque shielding (necessary after PT are removed and before reading is performed).
6. **Additional tests**
    a. **Repeat open application test** is performed by applying the antigen to the antecubital fossa, upper arm, or back skin twice daily for 1 week and observing for a reaction. A positive eczematous response is usually expected around days 2 to 4. Testing is stopped when the patient has a positive response. A reading performed at 15 to 30 minutes looks for contact urticaria. This approach is most applicable to "leave-on" products but not useful for "wash-off" products.
    b. **Skin biopsy** may be useful in diagnosing noneczematous conditions.

III. SPECIAL CONSIDERATIONS

A. Occupational contact dermatitis

More than 40% of worker's compensation cases involve skin disorders, and it is estimated that CD constitutes 90% to 95% of all occupational skin diseases. ICD is the most common type of contact dermatitis in the workplace and most frequently involves the hands and face.

IV. SPECIFIC ALLERGENS

A. Metals

1. **Nickel.** Nickel is the most common cause of ACD. It accounts for more positive reactions than all other metals combined. It is more common in adolescents, girls more than boys, and ear piercing is the most important predisposing factor. Nickel sensitization risk appears higher if piercing is obtained during childhood and increases with the number of body piercings. Data supports that intake of dietary nickel also contributes to vesicular hand eczema. Foods high in nickel include soybeans, cashews, figs, lentils, and raspberries. The presence of releasable nickel from the surface of any object can be detected using the dimethylglyoxime spot test; a pink color indicates the presence of releasable nickel.
2. **Gold.** Gold is frequently encountered as jewelry; however, other exposures include dental appliances, medications, and the electroplating industry. The most common sites of gold-related dermatitis include the hands, face, and eyelids. Women with titanium dioxide in cosmetics that adsorb gold released from jewelry are predisposed to gold dermatitis. Some patients with facial and eyelid dermatitis have had improvement with gold avoidance although the period of time and less-than-universal improvement with avoidance make this recommendation difficult to implement.

B. Cosmetics

Cosmetics and/or personal hygiene products are common sources of contact allergens. Although there are hundreds of chemicals contained within these products, a relatively small number of substances consistently cause ACD. These include fragrances, preservatives, base chemicals, adhesives, and sun blocks.

1. **Fragrances** are one of the most common causes of ACD in cosmetics. It is found in personal products, household products, and medicaments. Although “fragrance-free” products do not usually contain fragrance ingredients, those that are labeled “unscented” often have masking fragrances added. The “fragrance mix” that is frequently used for patch testing contains eight different fragrances and will detect approximately 85% of fragrance allergic individuals. Other fragrances tested include fragrance mix II, balsam of Peru, citronellol, and essential oils. The proper identification of the sensitizing fragrance that is responsible is essential to a meaningful program of avoidance. The current T.R.U.E. test includes balsam of Peru and fragrance mix I.

2. Balsam of Peru

In patients with fragrance-related systemic CD, a balsam-restricted diet can be considered; foods to avoid include citrus, flavoring agents (candy/ chewing gum), spices, chocolate, ice cream, colas, tomatoes, and perfumed or flavored teas.

3. **Preservatives** are present in most aqueous-based cosmetics and personal hygiene products. They are added to products to prevent rancidity and bacterial and fungal overgrowth and to extend shelf life. Preservatives can be grouped into those that release formaldehyde and those that do not (Table 11-11). Common sensitizers that are formaldehyde releasers include quaternium-15, diazolidinyl urea, DMDM hydraton, and imidazolindinyl urea, whereas thimerosal, benzalkonium chloride, and parabens are

nonformaldehyde releasers.

Table 11-11 Preservatives

Releasers of Formaldehyde	Nonreleasers of Formaldehyde
Diazolidinyl urea	Parabens
Imidazolindinyl urea	Methylchloroisothiazolinone
Quaternium-15	Methylisothiazolione
DMDM hydration	Methyldibromoglutaronitrile
Bromonitropropane	PCMX/PCMC
	Benzalkonium chloride
	Thimerosal

Formaldehyde is used in astringents, disinfectants, cleaning products, and metalworking fluids and is used widely in industrial procedures. Patients who are PT positive to formaldehyde should avoid contact with all of the formaldehyde releasers.

4. **Parabens** are nonformaldehyde releasers that are weak sensitizers in cosmetics. Patients who are paraben sensitive often tolerate paraben-containing cosmetics on normal intact skin and flare when the sensitizer is applied to sites of healed dermatitis.
5. **Lanolin** is an inert substance which serves to sequester, thicken, or lubricate the active component in a product. It can cause CD but can also act as an irritant at higher concentrations. Common exposures to lanolin are in personal-care products, clothing, and medications. However, medicaments containing lanolin are more sensitizing than lanolin-containing cosmetics. Lanolin is a weak sensitizer when applied on normal skin but a stronger sensitizer on damaged skin.
6. ***p*-Phenylenediamine**

   Hair products are second only to skin-care products as the most common cause of cosmetic allergy. PPD is part of permanent hair dyes and is the most common cause of ACD in hairdressers. The dermatitis secondary to hair dye usually is focused on the hairline, eyelids, and neck. Another exposure to PPD aside from hair dye is the addition of PPD to henna tattoos. PPD will also cross-react with other chemicals like PABA and padimate O (in sunscreens), sulfonamides, p-aminosalicylic acid, thia-zides, sulfonylurea, and celecoxib. IgE-mediated reactions like contact urticaria and anaphylaxis have also been attributed to PPD.

7. **Cocoamidopropyl betaine,** an amphoteric surfactant in shampoos, bath products, and cleansers, can also cause ACD on the eyelids, scalp, neck, and face. Positive PT results to this allergen are usually considered relevant.
8. **Sunscreens** may be used by themselves and are also frequently present in cosmetics such as moisturizers, "night" creams, lip and hair preparations, and foundation makeup. As a group, they are the most common cause of photoallergic contact dermatitis. "Chemical-free" sunblocks employ physical blocking agents instead of photoactive chemicals including titanium dioxide and zinc oxide, which rarely result in sensitization.
9. **Nail cosmetics** (including nail polish, artificial nails, and attachment glue) contain a number of sensitizing chemicals, including methacry-late ester monomers, dimethacrylates, and trimethacrylates, as well as cyanoacrylate-based glues. Clinical allergy to acrylics in nails can present locally at the distal digit or ectopically on the eyelids and face. Patch testing to a variety of acrylates and nail polish resin may be necessary to delineate the causative agent.

C. Rubber products

Contact dermatitis to latex allergens is traditionally believed to be secondary to rubber chemicals used in the manufacturing process. Rubber chemicals including thiuram mix, mercaptobenzothiazole, and mercapto mix are used in the manufacturing of rubber products including dipped (e.g., balloons, gloves) and molded (e.g., pacifiers) products. Contact reactions to products containing natural rubber, particularly gloves, may include ICD, ACD, and contact urticaria. Although ICD associated with rubber gloves is caused by irritation from hand washing, sweat retention, and friction, ACD is due to type IV hypersensitivity to accelerators used in the rubber-manufacturing process. Patients who are rubber allergic may have sensitivity to more than one antigen. There is cross-reactivity between carbamates and thiuram. Because ICD and ACD to rubber are difficult to distinguish on history or physical exam, an accurate diagnosis requires PT. Contact urticaria represents an IgE-mediated, immediate-type hypersensitivity reaction to latex rubber proteins and is best confirmed by *in vitro* tests measuring IgE to latex protein.

D. Topical medications

1. **Neomycin** was found to be the fifth most common allergen in North America in 2006. Its high rate of sensitization may be due to its frequent inclusion in over-the-counter topical antibiotic preparations. Higher risk patients include those who suffer from stasis dermatitis, leg ulcers, and patients with anogenital dermatitis. Positive PT results to neomycin are slow in appearance with peaks at days 4 to 7, but may then be persistent for weeks. Concomitant sensitization is seen with neomycin and bacitracin, and there is significant cross-reactivity with tobramycin, paromomycin, butirosin, framycetin, kanamycin, and gentamicin.
2. **Topical corticosteroids** (CS) contact allergy affects 0.5% to 5.8% of patients using these medications. PT to CS is complicated by the therapeutic anti-inflammatory nature of the CS itself, which may cause false-negative results. Risk factors attributed to the development of delayed

hypersensitivity to CS include chronic inflammatory skin disease (chronic venous leg ulcers, stasis dermatitis, contact dermatitis), patients with a history of ≥2 positive PT results, and multiple medicament sensitivities. Suspicion must arise for CD to CS when the dermatitis fails to respond to CS and/or when dermatitis worsens with treatment. Patch testing for CS allergy should include the groups of simultaneously or cross-reacting CS, as well as the vehicle and preservatives in the preparations. Topical CS is grouped structurally and cross-reactivity is based on two immune recognition sites, C 6/9 and C16/17 substitutions (Table 11-12). There is increased likelihood of clinical cross-reactivity of CS in the same group. Ninety percent of contact allergy to steroids will be detected by tixocortol pivalate, budesonide, triamcinolone, and the patient's commercial steroid. Thirty percent of ACD to CS would be missed without a late reading (day 7).

Table 11-12 Structrural Groups of Corticosteroids

Class A (Hydrocortisone and Tixocortol pivalate: has C17 or C21 short chain ester)
Hydrocortisone, -acetate, Tixocortol, Prednisone, Prednisolone, -acetate, Cloprednol, Cortisone, -acetate, Fludrocortisone, Methylprednisolone-acetate
Class B (Acetonides: has C16 C17 *cis*-ketal or -diol additions)
Triamcinolone acetonide, -alcohol, Budesonide, Desonide, Fluocinonide, Fluocinolone acetonide, Amcinonide, Halcinonide
Class C (nonesterified Betamethasone; C16 methyl group)
Betamethasone sodium phosphate, Dexamethasone, Dexamethasone sodium phosphate, Fluocortolone
Class D1 (C16 methyl group and halogenated B ring)
Clobetasone 17-butyrate, -17-propionate, Betamethasone-valerate, -dipropionate, Aclometasone dipropionate, Fluocortone caproate, -pivalate, Mometasone furoate
Class D2 (labile esters without C16 methyl nor B ring halogen substitution)
Hydrocortisone 17-butyrate, -17-valerate, -17-aceponate, -17-buteprate, Methylprednisolone aceponate

E. Plant-related CD

1. Plants of the *Toxicodendron* group, including poison ivy and poison oak, are common causes of allergic plant dermatitis in the United States.

Because of their potency, the clinical reaction typically results in vesicles and bullae, often with a characteristic linear pattern. The oleoresin can be transferred by handling exposed clothing, sports equipment, or even pet dander but not by the blister fluid. Soap and water inactivate the antigen. Rhus patch testing is not recommended due to its significant sensitizing capacity.

2. Compositae

Sesquiterpene lactone is an important allergen in the compositae (asteraceae) family of plants that are responsible for allergic contact plant dermatitis. These plants are used readily in herbal medicaments and cosmetics as they are valued as medicinal plants. Compositae sensitization is common in florists, farmers, and gardeners and in cosmetic dermatitis. The dermatitis has an airborne contact pattern distribution in the exposed areas of the hands and face with symptoms worse in late spring or summer and associated with picking daisies and dandelions or playing outdoors. CD to compositae should be suspected in patients with either personal or family history of atopy and exacerbated dermatitis in summer with plant exposure.

F. Biomedical devices

Allergic reactions to metals used in surgical implants, including cobalt, nickel, and chromium, can manifest as eczematous eruptions (localized or generalized) or with implant loosening. Reports suggest that allergy to metals, nickel in particular, may play a role in restenosis of endovascular stents. Contact dermatitis to orthodontic materials has been reported as well. More recently, reports of dermatitis to biomedical devices have lead to consultation request from orthopedic surgeons and orthodontists regarding safety of permanent or semipermanent metal medical devices in suspected nickel-sensitized patients. There has been a high variability of care in terms of testing and recommendations, and with at least 10% of the population being nickel allergic, this has increased health care costs. Medicolegal concerns contribute to testing consultations, and in some instances of joint replacement, selection of a more expensive and less durable option is done. As nickel allergy incidence increases, this problem also presumably will increase. The utilization of PT in these circumstances is fraught with controversy as it is poorly reliable in predicting or conforming implant reactions. The type and time of exposure is not the same for PT and orthopedic implants; the PT reading is at 48 to 96 hours, as opposed to weeks to months of exposure with an orthopedic implant. Also,

the haptenic potential of metals on open skin versus a closed periimplant environment is different. However, a negative PT is reassuring for absence of delayed hypersensitivity reaction. Unfortunately, once an allergic contact implant reaction has been determined, it must be removed and replaced with an implant free of the causative metal.

V. TREATMENT OF CD

A. Avoidance. The mainstay of treating CD is identification and discontinuation of contact with the offending agent. All other measures, including mechanical barriers and medications, only address symptomatic relief. The American Contact Dermatitis Society (info@contactderm.org) maintains a topical skin-care product database called the Contact Allergen Management Program (CAMP). Once the offending agents have been identified, a CAMP can be generated. This provides a safe list of products including cosmetics, hygiene products, and topical medications taking into account all relevant positive results obtained on PT and any cross-reactive agents. A list of potential exposure alternatives and substitutes to cosmetics should be offered to the patient to increase compliance.

B. Supportive measures. Cool compresses are usually soothing and mildly antipruritic. Topical diphenhydramine should be avoided because of the risk of cutaneous sensitization. In chronic eruptions, emollients used should be nonsensitizing and fragrance-free. Burrow solution (aluminum subacetate), calamine, and oatmeal baths can be utilized for relief of acute lesions. In nickel-allergic patients, barriers such as covers for metal buttons can be used. Garments containing formaldehyde should be washed prior to wearing. Excessive hand washing should be discouraged in patients with hand dermatitis and nonirritating moisturizers must be used after washing. Soaps and nonalkaline cleansers should be avoided.

C. Corticosteroids

Topical CS are first line in medical treatment for patients with CD. Low-potency CS are recommended for areas of thinner skin (particularly the face and eyelids), and high-potency CS are indicated for chronically thickened and lichenified lesions in other locations. Ointments are generally more potent and more occlusive and contain less sensitizing preservatives than creams and lotions. Systemic CS should be reserved for severe, acute cases, such as extensive *rhus* dermatitis (poison ivy). For extensive and severe CD, oral or parenteral systemic CS may offer relief within a day.

D. Immunomodulators. Evidence for the use of topical calcineurin inhibitors (pimecrolimus, tacrolimus) is limited in patients with ACD or ICD. These agents do offer the advantage of not causing skin atrophy and thus may be valuable in treating facial or eyelid dermatitis. One limiting factor has been a burning or stinging sensation with application. Oral immunomodulators such as cyclosporin, methotrexate, azathioprine, and mycophenolate mofetil can be considered in recalcitrant patients.

E. Oral antihistamines offer minimal relief from pruritus of CD. Physicians should not administer oral diphenhydramine in patients with CD to diphenhydramine in a calamine base (Caladryl) or hydroxyzine hydrochloride (Atarax) in ethylenediamine-sensitive patients.

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12

Urticaria and Angioedema

Jeffrey R. Stokes and Mark H. Moss

INTRODUCTION

Urticaria and angioedema are both symptoms and signs of specific diseases and independent disease classifications in their own right. For example, urticaria can be a sign of anaphylaxis when associated with signs and symptoms in other organ systems such as wheezing or hypotension. As a result, these diseases tend to be difficult to characterize by clinicians and patients alike resulting in confusion. Patients seek to have a definitive cause of their "hives," "whelps," or "welts" identified so that they can avoid and eliminate the trigger. Clinicians seek to identify or rule out known triggers to characterize urticaria and angioedema with a specific cause or to move on to classify the disease as idiopathic.

I. PATHOPHYSIOLOGY

Urticaria is caused by dilation of small venules and capillaries in the superficial dermis. The cutaneous mast cell is the primary cell involved in urticaria pathology. Classically, an antigen binds to high-affinity IgE receptors on the mast cell leading to the immediate release of mediators, such as histamine, prostaglandins, leukotrienes, and tryptase. A late inflammatory reaction occurs several hours after mast cell activation, leading to an increase in eosinophils, neutrophils, lymphocytes, and basophils at the site. The preformed mediator histamine is largely responsible for the classic wheal along with the flare response of vasodilation (erythema), increased vascular permeability (edema), and the axon reflex that increases this reaction via the neurotransmitter substance P. Substance P is a potent vasodilator that can stimulate further histamine release. Prostaglandin D2 is another vasodilator, while the cysteinyl leukotrienes, LTC4 and LTD4, increase vascular leakage and edema. All skin surfaces can be equally affected although urticaria can be more common on warmer body surfaces or areas compressed by clothing. Angioedema involves a similar mechanism but occurs in the deep dermis and subcutaneous tissue.

II. ACUTE/CHRONIC URTICARIA

A. Definition

Acute urticaria/angioedema lasts for <6 weeks, while chronic lasts 6 weeks or longer; however, some classification systems use 8 weeks as the cutoff between acute and chronic disease. Acute urticaria and angioedema are more frequently associated with identifiable causes, while chronic urticaria/ angioedema is more often associated with physical urticarias, presence of autoantibodies, or lack of an identifiable cause. Descriptive features of urticaria include a rash that is erythematous, raised, pruritic, blanchable, and generally transient with individual lesions lasting <24 hours. Chronic angioedema without urticaria may be

hereditary, acquired, or idiopathic and will be discussed separately.

B. Acute urticaria

1. Background

Acute urticaria is the most likely form of the disease to occur in pediatric patients and is often associated with recent viral infection or medication use. Acute urticaria occurs in as many as 15% to 24% of the US population at some point during their lifetime. Men and women are equally affected by acute urticaria, and all age groups are affected. Urticarial lesions are intensely pruritic and may be accompanied by angioedema in as many as 50% of patients. Patients often present to the emergency room or urgent/immediate care clinics due to the intense discomfort caused by the pruritus. Acute urticaria is self-limited lasting days to weeks. Although it lacks long-term consequences, urticaria is uncomfortable and significantly affects quality of life, causing anxiety and depression, and is frequently associated with sleep disturbance.

2. Causes

The most important information in identifying a cause of acute urticaria is a thorough history of the events occurring immediately preceding the appearance of the initial symptoms. Identifiable causes include foods; medications; insect stings; infections; contact with allergens such as latex, animals, and plants; and physical causes (Table 12-1).

Table 12-1 Common Causes of Acute Urticaria and Angioedema

Food allergy
Medication allergy
Latex allergy
Infection
Viral
Mycoplasma pneumonia
Bacterial
Parasitic
Insect sting/bite (papular urticaria)
Contact allergens (e.g., from animals and plants)
Physical triggers (e.g., pressure, etc.)

a. Foods

Readily identifiable exposure to foods should be explored in cases of acute urticaria where the patient or their family implicate a suspected food. This is in contrast to chronic urticaria where foods are much less frequently identified as a causative agent. The most common foods associated with urticaria in children are milk, eggs, peanut, soy, wheat, fish, and tree nuts and in adults are peanut, tree nuts, fish, and shellfish. The clinician should try to establish a temporal relationship between the suspected food and the onset of the urticaria. Usually, if a food is causative, the urticarial eruption will occur within 15 to 120 minutes of ingestion of the food, rarely hours later, and not on the following day. This temporal association should be reproducible upon reexposure to the suspect food. The history should guide very focused testing using a single food or small number of foods by skin prick testing (SPT) or blood immunoassay testing (RAST or CAP-FEIA) for food-specific IgE antibodies.

b. Medications

Medications cause numerous and varied reactions that may or may not be associated

with cutaneous findings. Urticaria is a frequent side effect associated with most medications but is most frequently encountered with antibiotics, typically in the beta-lactam family, and opiates. Nonsteroidal anti-inflammatory drugs (NSIADs), classically aspirin, can cause (or worsen) urticaria, although the specific mechanism is variable including both non-IgE and possibly IgE-related mechanisms. Latex has also been associated with acute contact urticarial responses. A detailed medication history including start and stop dates is essential as temporal cessation of a medication is often associated with urticaria resolution and reintroduction with a recurrence. However, drugs causing serum sickness can result in urticarial eruptions well after discontinuation. Specific questioning about over-the-counter medications such as aspirin or other NSAIDs is essential as patients typically do not mention them unless asked directly. Urticaria frequently, but not always, occurs shortly after a medication is initiated.

i. ACE inhibitors (Angiotensin-converting enzyme)

ACE inhibitors can cause urticaria but are most often associated with acute onset of potentially life-threatening angioedema within the first month of therapy. However, ACE inhibitor–associated angioedema can occur after months or even years of therapy. The angioedema associated with ACE inhibitors is likely due to impaired degradation of bradykinin typically leading to swelling of the face and tongue but can involve other areas. Most patients who have experienced ACE inhibitor–induced angioedema can safely use angiotensin receptor blockers without an increased risk of angioedema.

c. Infections

Infections are frequent causes of acute urticaria in children (usually a virus) and, to a lesser degree, adults. Urticaria may occur as part of a viral prodrome; however, it more often occurs or persists after the clinical infection has resolved, theoretically as part of a lingering immune response. Mycoplasma has been linked to acute urticaria but can progress to erythema multiforme. Case reports of localized bacterial infections in the sinuses, the lungs, and the prostate and dental abscesses have been associated with acute urticaria, but work-ups for unsuspected infections are unwarranted. Parasitic infection should be pursued as a possible cause when there is associated travel to endemic regions or exposure history. Fungal infections, including yeast, have been associated with acute urticaria, but again, this is a rare cause. Overall, if an infection is found, it is best to treat it, but this may not affect the urticaria.

d. Comorbid conditions

Autoimmune, lymphoproliferative, and endocrine disorders may also be associated with acute urticaria, although they are more likely associated with chronic urticaria. Papular urticaria of pregnancy (i.e., pruritic urticarial papules and plaques of pregnancy or PUPPs) is a self-limiting inflammatory condition seen in various stages of pregnancy presenting as an urticarial-like rash. It should also be noted that many patients with acute urticaria also have a component of physical urticaria and develop intensification of lesions at sites of constriction from clothing, with increased body temperature, heat exposure, or emotional distress.

C. Chronic urticaria

1. Background and definition

Patients with chronic urticaria have symptoms for more than 6 weeks. It is more likely to occur in adult patients but can occur in any age group. In general, the longer that the urticaria has been present, the less likely it is that a specific trigger will be identified. Chronic urticaria occurs in approximately 1% of the US population during their lifetime. Women are twice as likely to be affected. Urticarial lesions are intensely pruritic and may be accompanied by angioedema in as many as 50% of patients. Although chronic urticaria also lacks long-term consequences, it significantly affects quality of life affecting activities of daily living, social interactions, work, and sleep. Much like acute urticaria, the lesions of chronic urticaria can occur almost anywhere on the skin. While chronic urticaria can remit spontaneously with as many as 50% of patients finding resolution after 1 year, up to 20% of patients will continue to have urticaria for 10 years or longer.

2. Identifiable causes include autoimmune responses/diseases and physical triggers (Table 12-2). However, as much as 80% of chronic urticaria is idiopathic, without a definable cause. Seldom are acute viral illness, foods, medications, or other allergens triggers for chronic urticaria in contrast to acute urticaria.

Table 12-2 Causes of Chronic Urticaria

Autoimmune
Physical triggers
Dermatographic
Cholinergic
Cold associated
Acquired
Familial
Aquagenic
Solar
Vibratory
Delayed pressure
Idiopathic
Autoantibody
IgG antibody directed against the RcεR1α
IgG antibody directed against the Fc component of IgE antibody
Antithyroid antibodies (e.g., microsomal or antithyroglobulin)

a. Autoimmune

i. Classic autoimmune diseases such as SLE, Still's disease, Sjögren's syndrome, and dermatomyositis can present initially with urticaria. Patients with urticarial vasculitis may have associated JRA (juvenille rheumatoid arthritis), SLE (systemic lupus erythema-tosus), or hepatitis B or C. These patients usually present with lesions lasting more than 24 hours, and the individual lesions can be painful instead of pruritic.

b. Physical urticarias

Physical triggers cause 10% to 20% of chronic urticaria. These include dermatographic, cholinergic, cold-associated, aquagenic, solar, vibratory, and delayed pressure urticaria (Table 12-2). These physical factors may aggravate both acute and chronic urticaria or may be the primary cause of chronic urticaria.

i. Dermatographic

Dermatographism, or dermatographic urticaria, is the development of an urticarial

wheal at the site of physical pressure on the skin from scratching the skin or from tight clothing. This most common form of chronic urticaria affects between 4% and 5% of the general population. As a result of firmly stroking the skin, wheal-and-flare response develops. In comparison to other forms of urticaria, it is generally less pruritic.

ii. Cholinergic

Cholinergic urticaria is the development of small urticarial wheals (classically 1 to 3 mm in diameter) surrounded by large flares typically as a result of increased body temperature from physical activity. Cholinergic urticaria may account for up to 5% of all cases of chronic urticaria. Specific triggers often include hot baths and showers, exercise, sweating, and rarely anxiety. Cholinergic urticaria can range from being mildly pruritic and nonbothersome to life-threatening with systemic signs of anaphylaxis. Provocative testing includes exercise, hot water immersion, or a methacholine intracutaneous challenge test, although the negative predictive value of these tests is variable.

iii. Cold-induced (acquired and familial)

Cold-induced urticaria syndromes are characterized by the development of urticaria or angioedema following exposure to cold temperature. Although these conditions are generally benign, there are several instances reported of shock-like reactions during sudden immersion in cold water. Laryngeal edema has been reported after drinking cold beverages or eating cold food such as ice cream. Primary cold-induced urticaria is usually acquired, although there is a rare familial form. Patients with familial delayed cold urticaria develop urticarial lesions 9 to 18 hours after cold exposure, which then resolve as hyperpigmented skin lesions. Family studies suggest an autosomal dominant inheritance. Familial cold autoin-flammatory syndromes are distinct diseases and have nonurticarial rashes. Systemic disorders should be considered as potential causes for secondary cold-induced urticaria including cryoglobulinemia, mycoplasma infection, infectious mononucleosis, or vasculitis. Diagnostic testing for acquired disease is performed using the ice cube test. An ice cube or chip in a plastic bag is placed on the skin of the forearm for 5 minutes. During rewarming of the skin, erythema develops first and is followed by urticaria formation.

iv. Aquagenic

Aquagenic urticaria is the development of pinpoint hives (1 to 3 mm in diameter) precipitated by contact with water and is extremely rare. The lesions may occur with bathing/immersion or showering and is independent of water temperature. Diagnostic testing involves inducing urticaria at the site of placement of a wet compress, such as a washcloth, at 35°C on the upper body for 15 to 30 minutes.

v. Solar

Solar urticaria occurs on sun-exposed skin and usually occurs within minutes following exposure to sunlight or some forms of artificial light of the correct wavelengths. Lesions may develop under thin clothing. This physical urticaria is rare, with an estimated prevalence of 0.4%. Testing includes reproduction of lesions upon exposure to various light wavelengths. The differential diagnosis includes phototoxic

and photoallergic drug reactions, polymorphous light eruptions, and connective tissue disease.

vi. Vibratory

Vibratory angioedema is soft tissue swelling induced by vibration and rarely includes urticaria. Certain occupations such as manual laborers, carpenters, and metal grinders may find this problematic. Diagnostic testing is done using a vortex mixer on the forearm for 5 minutes measuring arm circumference before and after.

vii. Delayed pressure

Delayed pressure urticaria/angioedema involves soft tissue swelling several hours after prolonged pressure on the skin, such as on the feet, or after carrying a bag with a strap. Swelling that is deep and painful develops typically 6 to 8 hours after pressure but can be delayed up 12 to 24 hours and occur within 1 hour. Common triggers include wearing constrictive clothing, working with hand tools, hand clapping, standing for long periods of time, or sitting on a bench. Delayed pressure urticaria/angioedema may be present in a third of patients with chronic urticaria. In contrast to the mast cell predominance seen in other forms of chronic urticaria, histology shows an inflammatory infiltrate of neutrophils and eosinophils. There may be an associated low-grade fever, rigors, and malaise, with concomitant elevation in interleukin 6 (IL-6) and tumor necrosis factor (TNF). Patients with delayed pressure urticaria may be less responsive to antihistamine therapy. Diagnostic testing involves suspending a 15-lb weight over the patient's shoulder for 10 to 15 minutes. A positive response is defined as erythema, edema, and tenderness at the site at least 2 hours after the challenge.

c. Other possible etiologies

The ability of chronic infection to cause chronic urticaria has been reported. Possible infectious etiologies include Epstein-Barr virus, hepatitis, herpes simplex virus, and helminthic infections. Conflicting evidence has been reported for chronic sinusitis, onychomycosis, and *Helicobacter pylori* infection.

d. Idiopathic

In as many as 80% of cases of chronic urticaria, despite an extensive history, detailed physical examination, and exhaustive laboratory evaluation, an external cause is never identified. This is frustrating for both the patient and the clinician.

i. One subclass of chronic idiopathic urticaria is autoantibody-associated urticaria. As many as 30% to 50% of patients have an autoantibody-associated etiology for their chronic urticaria. The presence of a serum factor that caused wheal formation on intradermal injection of autologous serum was discovered in 1986. This autologous serum skin test (ASST) was observed in approximately 40% of the patients with idiopathic urticaria. The responsible factor was subsequently identified as an IgG antibody directed against the alpha chain of the high-affinity IgE receptor found on mast cells and basophils. An additional 5% to 10% of patients produce IgG antibodies directed against the Fc region of IgE. These antibodies appear to have a greater affinity for skin mast cells and do not usually provoke histamine release from mast cells found in the lung or gastrointestinal tract. Autoantibody-associated

urticaria is likely a result of cross-linking of IgE receptors resulting in activation and degranulation of mast cells. The presence of thyroid autoantibodies may be more frequently measured in patients with chronic urticaria; however, the role of these antibodies remains unclear.

D. Evaluation

1. History and physical examination

A detailed history including time of onset, timing of exposure to suspected triggers, and duration of symptoms is the most important element of the evaluation of the patient with urticaria and angioedema. A complete multisystem review of systems and physical examination should be performed. A description of any cutaneous lesions present should be noted. Consideration of a differential diagnosis for acute and chronic urticaria is helpful when obtaining the history and examination. For example, urticarial vasculitis may present with lesions lasting longer than 24 hours and include petechiae within and surrounding the urticarial lesions. The skin should be stroked with a tongue blade as part of the physical examination to document a dermatographic component to the urticaria. Examination of the thyroid may help delineate an autoimmune thyroid disorder or thyroid dysregulation. The lymphatic examination should include palpation of the liver and the spleen to evaluate for a lymphoma or hepatitis. Other areas of focus should include the musculoskeletal system and central nervous system. In summary, the medical history may give certain clues to the etiology of the urticaria, and the physical examination may offer the opportunity to further define and characterize the urticaria as well as limit the differential diagnosis (Table 12-3).

Table 12-3 Evaluation of the Patient with Urticaria

Detailed medical history
Physical examination
Testing for physical triggers
Laboratory
CBC with differential
ESR and/or CRP
Liver function tests
TSH +/– antithyroid antibodies
ANA[a]
Chronic urticaria index
Tryptase[a]
Stools O & P[a]
Autologous serum skin test

[a] When indicated by history or physical examination.

2. Testing for physical urticaria

Testing for physical urticaria should be guided by the history and focus on the individual suspected triggers. Multiple physical urticarias may occur in the same patient and represent the major etiology of chronic urticaria. Provocative diagnostic tests as outlined above should be done when a physical urticaria is suspected.

a. Laboratory evaluation

i. Acute urticaria

The laboratory evaluation should be directed by the history and physical examination.

Extensive skin testing or laboratory evaluation should be resisted as most testing in the absence of a guiding history or physical findings will be negative and lead to increased expense and confusion. Skin testing or blood immunoassay testing (RAST or CAP-FEIA) for allergen-specific IgE may be beneficial for confirming the etiology in acute urticaria when the history and physical examination point to a specific allergic trigger. Due to the possibility of false-positive results, random screening for food allergy as a cause for urticaria using a panel or large number of skin prick or immunoassay tests should be avoided.

ii. Chronic urticaria

1. *Baseline screening studies* to be considered include a complete blood count with differential (CBC with diff), erythrocyte sedimentation rate (ESR), and/or C-reactive protein (CRP), liver function tests, and thyroid stimulating hormone (TSH) to help identify causes of chronic urticaria. Antithyroid antibodies may support an autoimmune trigger. When autoantibody-associated urticaria is considered, one might perform an intradermal ASST. The ASST is performed by injecting 0.05 mL of the patient's serum into their forearm with appropriate intradermal saline controls. As the ASST is time intensive and requires sterile processing, it is infrequently performed. Further, a positive test result is not specific to chronic urticaria, and a negative test does not rule it out. More recently, a functional anti-FceR test or "chronic urticaria index" has become available. While a positive result supports an autoimmune basis of the urticaria, it does not indicate which autoantibody (anti-IgE or anti-FcεRI) is present nor does it currently guide prognosis or treatment selection.
2. *More specific laboratory tests* should be selective and based on diagnostic suspicions, for example, a latex IgE evaluation for health care workers, or an ANA (antinuclear antibody) for the patient with an elevated ESR or where systemic lupus erythematosus or urticarial vasculitis is suspected. A tryptase level can be useful in suspected mastocytosis. In an older patient with weight loss and lymphadenopathy, one may wish to rule out a lymphoma or a monoclonal gammopathy. Hepatitis B and C antigen titers may be associated with cold-induced urticaria and cryoglobulinemia. If there is a history of travel to a parasite endemic region, one may wish to obtain a stool specimen for ova and parasites.
3. *SPT and immunoassay testing* to allergens including aeroallergens and foods are seldom helpful in the evaluation of chronic urticaria and should be avoided.
4. *Complement evaluations* are most helpful in the diagnosis of angioedema and may be normal or slightly low in urticarial vasculitis.

b. Biopsy

A typical individual wheal in urticaria is pruritic and transient, generally lasting <24 hours. If wheals last longer than 24 hours and are associated with pain, burning, or bruising, a biopsy should be considered to exclude urticarial vasculitis. Skin biopsy may also be useful when cutaneous mastocytosis is suspected. Biopsy can also be considered if the patient is refractory to treatment to better guide further therapeutic recommendations.

E. Treatment

1. Avoidance: Avoidance of known triggers of urticaria is possible with acute urticaria,

especially when it is related to foods or medications such as antibiotics. Avoidance of other medications that can exacerbate urticaria/angioedema such as ACE inhibitors, opioids, alcohol, and NSAIDs is an easy first step. For chronic urticaria, avoidance of foods and medications generally is ineffective though some question using a pseudoallergic food diet to avoid all preservatives or food additives. This has shown some benefit in studies, but given the lack of consistent provocation responses to the pseudoallergens and the difficulty in achieving a preservative-free diet, this has not been universally recommended. For physical urticarias, avoiding specific provocative stimuli such as cold for cold-induced urticaria, tight clothing for dermatographism, and delayed pressure urticaria or heat for cholinergic urticaria is helpful (Table 12-4).

Table 12-4 Therapy for Urticaria/Angioedema

First step: avoidance of known triggers
Second step: H1 antihistamines
Second-generation H1 daily dosing
Third step: higher doses if H1 antihistamines
Second-generation at 2–4× the typical daily dose
Two different second generation antihistamines, AM and PM dose
Morning second-generation antihistamine, bedtime first-generation antihistamine
Fourth step: additional therapies
H2 antihistamines
Doxepin at bedtime
Leukotriene modifier
Fifth step: Severe episodes, systemic corticosteroids (try to limit use and duration)
Sixth step: Alternative, steroid-sparing agents
Anti-inflammatory agents
Immunosuppressants
Biologic agents

2. **Systemic diseases:** Treating autoimmune diseases that have urticaria as an early symptom, such as SLE, should be undertaken. With clinical thyroid disease such as Hashimoto's or Graves' disease, therapy for the primary disease may be all that is needed for resolution of the urticaria. The use of thyroid replacement in euthyroid patients with thyroid autoantibodies only is generally ineffective.

3. **Infections:** Viral infections such as hepatitis, infectious mononucleosis, coxsackievirus infection, mycoplasma infection, and helminthic infections are common causes of acute urticaria and are often self-limiting, so only supportive care is needed. Treating chronic infection such as *H. pylori*, sinusitis, or onychomycosis has been effective in some patients with chronic urticaria.

4. **Antihistamines:** Oral H1 antihistamines are the first-line therapy for acute and chronic urticaria.

    a. H1

    i. **First generation:** First-generation H1 antihistamines (diphen-hydramine, hydroxyzine, chlorpheniramine, cyproheptadine, and promethazine) have historically been the initial therapy for urticaria given the predominant role of histamine in the pathogenesis of urticaria/angioedema. Due to the ability of these medications to cross the blood–brain barrier, systemic side effects such as sedation and performance impairment are common. Tolerance to the sedating effects may develop with regular

use with standard dosing. Anticholinergic side effects such as dry mouth and urinary retention are frequent, especially in children and the elderly. The relatively short half-life of these medications often requires dosing four times a day, unlike the daily second-generation antihistamines. Cyproheptadine specifically has been used effectively for cold-induced urticaria.

ii. **Second generation:** The oral second-generation antihistamines (cetirizine, levocetirizine, loratadine, desloratadine, and fexofenadine) have minimal sedating or anticholinergic side effects. Current evidence demonstrates that second-generation antihistamines may have some mild anti-inflammatory properties. Second-generation antihistamines are the preferred first-line therapy, and first-generation antihistamines should generally be avoided. Prophylactic daily dosing is more effective than as-needed dosing for improving quality of life in patients with persistent urticaria/angioedema. Doses up to four times the standard dose have been well tolerated and effective for chronic urticaria. Some second-generation antihistamines can cause sedation at these levels but generally still less than the first-generation medications. Other regimens besides increasing the dosing of one antihistamine include using two different types of second-generation antihistamines, a morning and evening medication, or a second-generation H1 antihistamine in the a.m. and a first-generation at bedtime. Using a first-generation antihistamine at night may lessen sleep disturbances due to itching secondary to the sedating effect but can cause morning impairment.

b. H2

Adding H2 antihistamines (cimetidine or ranitidine) with H1 antihistamines in chronic urticaria daily to bid can improve some patients with chronic urticaria but are not effective as monotherapy. This improvement varies from patient to patient, but given the excellent safety profile of H2 antihistamines may be worth a trial.

5. **Doxepin**, a tricyclic antidepressant, is a potent histamine H1 and H2 receptor antagonist. Doxepin at doses up to 50 to 100 mg at bedtime, less than therapeutic antidepression doses, may be effective in refractory urticaria, but use is limited by sedation effects even when dosed at night.
6. **Corticosteroids** are effective for acute urticaria and beneficial for chronic urticaria, but due to their side effects and rebound tendency are not recommended for long-term use. In some cases, short-term use (1 to 3 weeks) may be necessary to gain immediate control until other therapies can maintain the improvement.
7. **Self-injected epinephrine** may be used for acute attacks, especially when laryngeal edema is present.
8. **Alternative therapy:** As many as 50% of chronic urticaria patients may not receive adequate control with antihistamine therapy.

a. Leukotriene-modifying agents such as montelukast and zafirlukast have limited usefulness in refractory chronic urticaria. However, since they have a good safety profile, this may be a better initial option before using other medications with associated side effects. Benefits with physical urticarias, such as delayed pressure and cold urticaria, as well as NSAID-exacerbated chronic urticaria, have been reported.

Patients with autoantibodies may be more responsive to this therapy. Generally, leukotriene modifiers are added on to antihistamine therapy and are not recommended as monotherapy.

b. Anti-inflammatory agents: There are limited data for efficacy, but they may be valuable in treating refractory chronic urticaria and urticarial vasculitis. Dapsone and colchicine may also be effective in neutrophilic urticarial vasculitis.

i. Dapsone. Requires monitoring for anemia, including prescreening for glucose-6-phosphate dehydrogenase deficiency to prevent hemolytic anemia.

ii. Sulfasalazine. Early in therapy, nausea, vomiting, and headache occur in patients on high-dose therapy. Blood and urine monitoring are necessary for potential side effects of therapy.

iii. Hydroxychloroquine. Patients have a risk of retinopathy, and thus ophthalmic evaluations are necessary.

iv. Colchicine. Most common side effect is diarrhea, while high doses can lead to bone marrow suppression and long-term use has been associated with myopathy.

c. Immunosuppressants: Immunosuppressants are capable of inducing remission, but the quality of evidence to support their use is low. They are generally reserved for oral steroid–dependent chronic urticaria patients.

i. Cyclosporine. Patients require careful monitoring. Due to different bioavailability between different cyclosporine preparations, various formulations cannot be used interchangeably. Side effects are common with treatment, with increasing serum creatinine noted in 10% of urticaria patients treated with cyclosporine.

ii. Tacrolimus. In theory may be a safer alternative to cyclosporine, but data are limited.

iii. Mycophenolate. Up to 20% of patients have GI side effects, while a less common finding is reversible leukopenia.

iv. Sirolimus has been associated with angioedema.

d. Biologic agents

i. Omalizumab has been effective in isolated cases of chronic idiopathic, cholinergic, cold-induced, delayed pressure, and solar urticaria. Large phase III clinical trials are ongoing for chronic urticaria.

ii. IVIG has been used for delayed pressure, solar, and idiopathic urticaria with limited success.

Other agents include anti-TNF agents (etanercept, infliximab); IL-1 receptor antagonist (anakinra), which is especially useful for familial cold autoinflammatory syndrome; and anti–B cell therapy (rituximab).

e. Other therapies for chronic urticaria include methotrexate, oral beta agonists, androgens for hereditary angioedema, nifedipine, plasma-pheresis, and phototherapy, which may be beneficial in solar urticaria to induce tolerance. However, these therapies are considered experimental and should only be used by specialists familiar with their use.

III. ANGIOEDEMA ONLY

A. Hereditary

1. **Background/presentation:** Hereditary angioedema (HAE) is an autosomal dominant disorder caused by a deficiency in the C1 esterase inhibitory protein. The prevalence is estimated at 1 in 30,000 to 80,000. Patients present with unpredictable episodic, nonpruritic localized angioedema without urticaria, typically involving limbs, lips, face, tongue, genitalia, and larynx. No urticaria is present, but patients can have erythematous mottling, or erythema marginatum. Generally, these erythematous rashes are mild and precede angioedema episodes. Abdominal attacks can mimic bowel obstruction or appendicitis. Patients with frequent abdominal attacks may have associated H. pylori. Extremity or facial reactions can be misdiagnosed as an allergic reaction, but urticaria is absent in HAE. The mean number of attacks if untreated is 1 every 2 to 3 weeks, typically resolving in 48 to 72 hours, with symptoms often worsening over the first 24 hours. Episodes can be as infrequent as a few attacks in a lifetime or as frequent as several times a week lasting as briefly as 4 hours or up to 1 week. About half the patients will have laryngeal edema during their lifetime. Typical triggers include trauma, stress, cold, infections, and dental procedures. In about 50% of patients, symptoms manifest prior to puberty, while another one-third by 20 years old. Approximately 75% of patients have a positive family history (Table 12-5).

Table 12-5 Evaluation of Complement Proteins for Angioedema

Type	Pattern	C1-INH Function	C1q Level	C4
HAE I	Late childhood, early adulthood, recurrent family history 75% cases	Decreased (<30%)	Normal	Decreased
HAE II	Late childhood, early adulthood, recurrent family history 75% cases	Normal	Normal	Decreased
HAE III	Women	Normal	Normal	Normal
Acquired	Middle age, no family history	Normal	Normal	Decreased (<30%)
Allergic	Specific exposures, with urticaria	Normal or decreased	Normal	Normal
ACE inhibitor associated	Use of ACE I medications, typically face and tongue	Normal	Normal	Normal

2. **C1 inhibitor:** The C1 inhibitor (C1-INH) is a serine protease inhibitor that breaks down C1r and C1s, factors Xia and XIIa, and kallikrein. Decreased C1-INH leads to increased kallikrein activity and subsequent increased bradykinin levels. Bradykinin typically acts on BK2 receptor on endothelial cells to mediate angioedema. Low levels of C2 and C4 are present due to uncontrolled activation and consumption of these early complement components even during asymptomatic periods.
3. Three types of HAE have been identified:
   - **a.** Type I HAE accounts for up to 85% of the cases and is due to low levels of C1 inhibitor. The functional level is low in proportion to the low levels of protein.
   - **b.** Type II HAE has normal levels of C1 inhibitor but abnormal protein activity accounting for up to 15% of HAE patients.

c. Recently a rare form of HAE, type III HAE, has been described predominantly in women presenting with recurrent facial edema usually after oral contraceptive use or pregnancy. This type is also autosomal dominant but has normal C1-INH levels and function of C1-INH. Key mutations in the factor XII (Hageman's factor) gene seem to be the cause for the angioedema in a subgroup of these patients due to increased bradykinin signaling.

4. **Treatment:** Unlike allergic urticaria and angioedema, epinephrine, cor-ticosteroids, and antihistamines are ineffective in treating acute attacks.

a. Fresh frozen plasma (FFP): Infusions of FFP replenishes C1-INH but can worsen an episode as the plasma proteins and kinins are also supplied. It is a blood product with typical concerns of all blood products of transmission of infection. The use of two units of FFP has been used effectively as prophylaxis before dental procedures.

b. Androgens: Male androgens (stanozolol and danazol) increase endogenous production of C1-INH and decrease the formation of bradykinin while increasing its degradation. Stanozolol is no longer available in the United States, and androgens are contraindicated in most children due to effect on bone growth. In addition, androgens cannot be used in pregnancy due to possible masculinization of fetus. Side effects of therapy are a major issue including virilization, hepatotoxicity, weight gain, hypertension, acne, dyslipidemia, abnormal liver function, hematuria, myopathy, headaches, abnormal menses, decreased libido, anxiety, and hair loss.

c. Antifibrinolytic agents such as tranexamic acid are less effective than androgens but are not approved for use in the United States. Frequent nausea, diarrhea, vertigo, muscle cramps, and increased in thrombosis have all been reported with therapy.

d. C1 esterase inhibitors: The C1 inhibitor protein is available as a plasma product that has either been treated by nanofiltration or pasteurization, to prevent transmission of blood-based viruses such as hepatitis C.

i. The pasteurized plasma-derived C1-INH, Berinert, was approved by the FDA for treatment of acute attacks in 2009. Studies demonstrated improvements in abdominal and facial swelling in 30 and 90 minutes. This requires intravenous infusion of 20 units/ kg and has been used in Europe for over 25 years.

ii. In 2008, the nanofiltered plasma-derived C1-INH product Cinryze was approved for prophylactic use in the United States, dosed as 1,000 U intravenously every 3 to 4 days. Studies demonstrated reduction in number of days swollen, severity of attacks, and duration of attacks. Currently, Cinryze is being evaluated for acute attack relief.

iii. A recombinant C1 inhibitor, Rhucin, is currently being evaluated in the United States for acute attacks. The protein is produced in transgenic rabbits and purified from their milk. Early studies demonstrated improvement in median time for symptom relief compared to placebo when given parenterally. One episode of drug-associated anaphylaxis was noted in a patient allergic to rabbit epithelium.

e. Ecallantide (Kalbitor) is a kallikrein inhibitor protein approved by the FDA for acute attacks in 2009. Kallikrein is regulated by C1-INH and affects vascular permeability. Studies demonstrated ecallantide leads to sustained improvement 4 hours after dosing 30 mg subcutaneously in cutaneous, abdominal, and facial attacks.

Anaphylaxis due to administration has been noted within an hour in 3% to 4% of patients. In these patients, it may be difficult to delineate the angioedema from HAE versus anaphylaxis.

f. Bradykinins are key mediators in tissue angioedema. A selective second-generation bradykinin B2 receptor inhibitor, Icatibant (Firazyr), given subcutaneously for acute attacks, has been approved for treatment in Europe since 2008 but not yet approved in the United States. Some studies have demonstrated improvement in symptom severity within 2 to 2.5 hours. Local injection site reactions are common but transient.

B. Acquired: Acquired angioedema patients have hyperactivation of classic complement cascade and thus decreased C1q levels. Acquired C1 inhibitor deficiency can be due to presence of circulating autoantibodies against C1-INH or increased catabolism of the protein. Type I acquired angio-edema is frequently seen in underlying lymphoproliferative diseases such as malignancy (B-cell lymphoma, prostate cancer, CLL, and monoclonal gammopathies of undetermined significance). Type II acquired angioedema appears to be due to autoantibodies to C1-INH. Both types typically present in the elderly. Patients with acquired C1-INH deficiency respond to antifibrinolytics with a decreased response to C1 inhibitor replacement therapy.

IV. SUMMARY

Episodes of urticaria/angioedema can be isolated or as a symptom of another disease process. Careful evaluation requires knowledge of the causes of both acute and chronic urticaria/angioedema. The most important tool for diagnosis is a thorough history of the episodes. Physical exam and subsequent testing are beneficial in confirming potential triggers and etiologies identified by the history. Once identified, trigger avoidance is the easy first step in treatment. Frequently, triggers and causes may not be found and medical therapy is indicated. Antihistamines are the mainstay of treatment but may require higher-than-normal dosing to give symptom relief. When not sufficient, alternative therapies may be necessary with the focus on the risk and benefit of each type of treatment. In patients with isolated angioedema, laboratory evaluation is necessary to clarify hereditary causes from acquired. Recent developments in treatment for hereditary angioedema have given the clinician better therapies to improve the quality of life for these patients, both preventatively and for life-threatening attacks.

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13

Anaphylaxis

Phil Lieberman and Debendra Pattanaik

I. DEFINITION

The classic definition of anaphylaxis is "An acute, systemic, immediate hyper-sensitivity reaction caused by IgE-mediated immunologic release of mediators from mast cells and basophils."

Clinically similar events not mediated through IgE have been called anaphy-lactoid reactions. More recently, it has been suggested that the term "anaphylac-toid" be abandoned, and all events, regardless of the mechanism of production, be called anaphylactic episodes. Thus, the new definition of anaphylaxis would include events that are IgE mediated plus those that are non-IgE mediated.

II. INCIDENCE

The exact incidence of anaphylaxis is unknown, but based on data gleaned from real-time prescriptions for automatic epinephrine injectors, as much as 1% of the population may be at risk for anaphylaxis. Anaphylactic episodes appear to be increasing in frequency. The risk factors that predispose an individual to anaphylaxis are the presence of atopy, asthma, and, in adults, prior to menarche, female gender. In addition, geographic location seems to play some role in that episodes have been reported to be more frequent in higher latitudes in the upper hemisphere and lower latitudes in the lower hemisphere (thus increasing in frequency with diminishing exposure to sunlight).

III. PATHOPHYSIOLOGY

The degranulation of mast cells and basophils is the primary event underlying anaphylactic episodes. The mediators released from mast cells and basophils include histamine, neutral proteases, proteoglycans, chemoattractants, nitric oxide, interleukins, and other cytokines. For a detailed discussion of these mediators, please see the chapter on Immediate Hypersensitivity. The sum total of the effects of these mediators is to produce vasodilatation, increased vascular permeability, smooth muscle constriction, irritation of afferent sensory nerves, and chemotaxis.

IV. CLINICAL MANIFESTATIONS

A. Symptoms

The clinical manifestations of anaphylactic events are seen in Table 13-1, which lists them by incidence. Cutaneous and subcutaneous manifestations are the most common. In adults, 90% or more of patients experience cutaneous manifestations characterized by urticaria, pruritus, or flush. The incidence of these in children appears to be slightly lower. Respiratory complaints occur next most commonly. They consist of wheeze, shortness of breath, stridor, and cough. They occur in about 40% to 60% of cases. They are a risk factor for mortality. Cardiovascular

symptoms are the next most frequent manifestation. They consist of hypotension, arrhythmia, dizziness, syncope, angina, and myocardial infarction. They appear in 30% to 35% of events overall. They are more common in adults. Gastrointestinal symptoms appear at about the same frequency as cardiovascular manifestations. They include nausea, vomiting, cramping abdominal pain, and diarrhea. They seem to be more frequent if the antigen has been ingested versus injected. Symptoms of anaphylaxis usually begin 5 to 30 minutes after antigen injection and within 2 hours after antigen ingestion. However, there can be a delay of several hours after ingestion in some instances. It is felt that the more rapid the onset of symptoms after exposure to allergen, the more severe the event.

Table 13-1 Signs and Symptoms of Anaphylaxis

Cutaneous, subcutaneous
Urticaria and angioedema
Flush
Pruritus without rash
Respiratory
Wheeze
Dyspnea
Upper respiratory obstruction (angioedema)
Rhinitis
Cardiovascular
Dizziness
Syncope
Hypotension
Arrhythmia
Angina
Myocardial infarction
Gastrointestinal
Nausea
Vomiting
Diarrhea
Cramping abdominal pain
Miscellaneous
Headache
Substernal pain
Seizure
Disseminated intravascular coagulation

It should be noted that some patients do not present with "classical" manifestations as described above. Perhaps the most common atypical presentation is cardiovascular collapse with shock in the absence of other symptoms or signs. A significant percent of such patients express neurologic manifestations including seizures and muscle spasms. Asthmatic children with food allergies can have episodes that begin initially with only asthma.

Of course, respiratory reactions and cardiovascular reactions are responsible for the majority of fatalities. Upper airway obstruction as well as asthma can result in fatal events. Shock and myocardial infarction due to coronary artery vasospasm are also causes of fatal reactions.

B. Duration of anaphylaxis

Anaphylactic episodes can be uniphasic, biphasic, or protracted. Uniphasic events usually have a rapid onset, and symptoms subside within an hour or two and do not return. Biphasic events are characterized by a recurrence of symptoms after resolution of the initial episode. Protracted events can last hours and, in rare instances, even days. The exact incidence of each type of event is unknown. Uniphasic events are clearly the most common however. Biphasic events have been estimated to occur from 1% to 20% of episodes. The majority of these

appear within 8 hours after resolution of the initial symptoms, but such events can be delayed as long as 24 hours and rarely even longer. Because of the clinical significance of biphasic reactions in terms of the suggested length of patient observation after an initial resolution of symptoms, it is important to be aware of the risk factors for biphasic events. Factors that have been cited that increase the risk of a biphasic event are the presence of hypotension during the first phase, the failure to administer epinephrine or a delay in its administration, and an event due to an ingested (vs. injected) antigen, especially food.

V. SUBSTANCES CAUSING ANAPHYLACTIC EPISODES

The most common causes of anaphylactic events are seen in Table 13-2. Foods are probably the most common cause of anaphylaxis overall and are certainly the most common cause in children. Of these, milk, egg, wheat, soy, peanut, and tree nut produce the majority of reactions in children, and shellfish, fish, and peanut are the most common food offenders in adults. However, overall, in adults, medications rival food as the most common cause of anaphylactic events. The most common of these are beta-lactam antibiotics, and the next most common are nonsteroidal anti-inflammatory drugs (NSAIDs). It is important to note that in published series of adults experiencing anaphylaxis, the majority of events are idiopathic.

Table 13-2 Frequently Reported Causes of Immediate Generalized Reactions

Causative Agent	Mechanism
Foods	IgE mediated
Nuts	
Legumes (peanuts)	
Shellfish	
Egg whites	
Milk	
Pistachios, cashews	
Seeds (mustard)	
Insect venoms	IgE mediated
Wasps	
Hornets	
Honey bees	
Yellow jackets	
Fire ants	
Proteins or peptides	
Streptokinase	IgE mediated
Insulin	IgE mediated
Seminal plasma	Some IgE mediated
Allergen immunotherapy vaccines	IgE mediated
Latex	IgE mediated
Muscle relaxants	Mast cell activation (some IgE mediated)
Antibiotics	
Penicillins	IgE mediated
Cephalosporins	IgE mediated
Sulfamethoxazole	Some IgE mediated
Trimethoprim	Some IgE mediated
Fluoroquinolones	Unknown
Vancomycin	Mast cell activation
Diagnostic agents	
Radiocontrast media	Unknown
Gadolinium	Unknown
Fluorescein dye	Unknown
Procedure related	
Dialyzer membranes	Complement activation
Plasma (including platelet infusions)	Complement activation (some IgE mediated)
Intravenous immunoglobulin	Complement activation, IgG or IgE mediated
Miscellaneous	
Monoclonal or chimeric antibody	Likely IgE mediated
Aspirin, nonselective NSAIDs	Leukotriene D_4 production; suppression of prostaglandin E; mast cell activation
Angiotensin-converting enzyme inhibitors	Bradykinin potentiation
Exercise-induced anaphylaxis	Unknown
Exercise plus food-induced anaphylaxis	Unknown
Idiopathic anaphylaxis	Unknown

IgE, immunoglobulin E; NSAIDs, nonsteroidal anti-inflammatory drugs.

VI. COMMON TYPES OF ANAPHYLAXIS

A. Natural rubber latex–induced anaphylaxis

Three groups of individuals are at high risk of developing sensitivity to latex. These include children with spina bifida and genitourinary abnormalities, workers with occupational exposure to latex, and health care workers. Latex-induced anaphylaxis can occur in a variety

of situations including direct contact with latex (this is usually via gloves and also condoms) or by aerosolization of latex antigen adhered to corn starch from the powder of latex gloves. Thus, one of the most common settings for latex reactions is in surgery. Latex reactions in this setting have also been reported due to the administration of a drug through a latex port. Latex anaphylaxis has become less common as the use of powdered latex gloves in health care settings has declined. It still, however, remains a problem in the other two groups of at risk individuals. Unfortunately, there is no standardized skin test for latex available in the United States today. However, there is a test for serum-specific IgE to latex. If the *in vitro* test is positive, there is a high clinical likelihood that latex sensitivity is present. In contrast, a negative test does not rule out latex sensitivity. Patients with a diagnosis of latex allergy should wear a medical identification bracelet. If there is any chance of exposure, they should also carry an automatic epinephrine injector. Patients with latex sensitivity should be instructed to notify all their health care providers including dentists of their sensitivity. Surgical procedures should be done in latex-free operating rooms, and precautions should also be taken during dental visits.

B. Exercise-induced anaphylaxis

Exercise-induced anaphylaxis has been reported due to almost any form of exercise including jogging, racket sports, aerobics, dancing, brisk walking, and weight lifting. Cessation of the exercise usually rapidly improves symptoms, but if exercise is continued, symptoms will progress. Fatal reactions to exercise-induced episodes are probably rare, but there has been at least one death. Many patients with exercise-induced anaphylaxis require cofactors. That is, exercise alone is insufficient to produce the reaction. The most common cofactor is the ingestion of a specific food to which the patient is allergic. In some patients, eating itself, regardless of the food, can be a cofactor. Other cofactors include drugs, especially NSAIDs, alcoholic beverages, menstruation, and seasonal pollen exposure. Neither the exercise nor the specific cofactor alone will produce an event, but if exposure is associated with exercise, the reaction will occur.

The diagnosis of exercise-induced anaphylaxis is made by history. An exercise challenge can be performed, but for reasons unknown, responses can be inconsistent. When a patient does have exercise-induced anaphy-laxis, it is important to identify cofactors on the basis of history, and allergy skin testing is also recommended when the history is suggestive. Exercise-induced anaphylaxis should be distinguished from cholinergic urticaria. In the latter condition, the event is induced by elevation of body temperature sufficient to cause sweating. Exercise therefore is one of the triggers. However, other triggers that raise body temperature such as a hot shower can also produce an event. In addition, the appearance of the urticaria differs between these two entities. Cholinergic urticaria is characterized by pinpoint wheals that can progress and coalesce to giant hives. In exercise-induced anaphylaxis, giant hives usually appear as one of the first signs.

Strategies to prevent exercise-induced anaphylaxis must be individualized. The patient should always have immediate access to autoinjectable epinephrine whenever they exercise. Patients should be advised to exercise with a partner. In those patients where a cofactor has been identified, exposure to this cofactor should be avoided when the patient is exercising. At the first sign of symptoms, the patient should stop exercising immediately. Pharmacologic therapy for prevention has produced

inconsistent results. There is no definite evidence that oral antihistamines or corticosteroids will have a beneficial effect.

C. Idiopathic anaphylaxis

A group of patients (in fact as many as 60% of cases in adults) will experience repeated episodes of anaphylaxis without any identifiable cause. Regardless of how intensively such patients are evaluated, no cause can be determined. The symptoms are identical to those that are found in other causes of ana-phylaxis. Mast cell degranulation is certainly involved, since patients do exhibit elevated tryptase and also increases in urinary histamine metabolites.

The diagnosis of idiopathic anaphylaxis is clinical and relies upon the exclusion of other causes. Therefore, patients should receive a careful evaluation with emphasis on the history and events surrounding the episodes. Selective skin testing to foods (sometimes employing fresh foods rather than commercial extracts) and/or tests for serum-specific IgE to foods are indicated. Systemic mastocytosis should be ruled out. Patients with episodes of idiopathic anaphylaxis should be evaluated with a baseline serum tryptase, and if the tryptase level is elevated, a bone marrow biopsy should be considered.

Many daily preventive regimens have been suggested. Patients have been treated with daily oral corticosteroids, H1 antagonists, and a combination of H1 and H2 antagonists. The studies have for the most part shown that such daily treatment can be helpful but most often does not control the episodes completely. Particular care must be taken with chronic administration of oral corticosteroids because of side effects. Fortunately, the prognosis is usually good for such patients. The majority experience a diminished frequency of episodes as time progresses.

D. Radiocontrast media

The vast majority of radiocontrast media reactions are probably due to the direct effect of radiocontrast on mast cells and basophils and do not appear to be IgE mediated. Anaphylactic episodes to radiocontrast media have declined markedly since the advent of agents that are iso-osmolar. Atopic patients are predisposed to such reactions. It was originally hypothesized that patients allergic to shellfish were predisposed, incorrectly attributing the reaction to "iodine" present both in shellfish and radiocontrast. However, iodine is not involved in the pathogenesis of these events. It does happen, however, that atopic individuals are more prone to these events, not patients with shellfish allergy in particular, but those with atopy in general. The reason for this has not been completely established, but it is hypothesized that atopic individuals have a lower threshold for degranulation (not only to radiocontrast but to other direct-acting mast cell secretagogues as well).

Most such events can be prevented by a pretreatment regimen. The most commonly prescribed pretreatment regimen consists of prednisone 50 mg PO q 6 h beginning 18 hours before the procedure and diphen-hydramine 50 mg IM 1 hour before the procedure. This regimen is recommended for an individual who has had a previous anaphylactic reaction to radiocontrast who must receive this diagnostic agent again. In addition, an iso-osmolar agent should be utilized. A nonionic, iso-osmolar dimer is probably the drug of choice when radiocontrast must be administered to a patient who has experienced a previous reaction.

E. Systemic mastocytosis

Systemic mastocytosis can be a cause of severe episodes of anaphylaxis, and these episodes usually present as idiopathic events. However, they can clearly be triggered by agents known to degranulate mast cells, especially opioids. In its classic form, systemic mastocytosis is due to a gain-of- function tyrosine kinase mutation in the c-kit receptor (a growth receptor on the mast cell), which produces an autoactivation of the receptor, resulting in spontaneous mast cell degranulation. Such patients also have characteristic bone marrow findings. Recently, patients who are clinically indistinguishable from classical mastocytosis patients have been described as those who do not have all the classic biopsy findings for this condition. A term entitled "mast cell release syndrome" or "mast cell activating disorder" has been applied to this group of patients. There is no definitive therapy at present available for patients with mastocytosis. They are treated in a similar fashion as patients with idiopathic anaphylaxis to prevent bothersome symptoms (such as urticaria) or life-threatening events.

VII. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of anaphylaxis is summarized in Table 13-3.

Table 13-3 Differential Diagnosis of Anaphylaxis

- Anaphylaxis due to exogenously administered agents (e.g., drugs, foods)
- Anaphylaxis due to physical factors
  - Exercise
  - Cold
  - Heat
  - Sunlight
  - Idiopathic anaphylaxis
- Vasodepressor reactions
- Flush syndromes
  - Carcinoid
  - Postmenopausal
  - Alcohol
  - Drugs
  - Niacin
  - Vasointestinal polypeptide–secreting tumors
  - Medullary carcinoma thyroid
  - Gastrointestinal tumors
- Other forms of shock
  - Cardiogenic
  - Hemorrhagic
  - Endotoxic
- "Restaurant syndromes"
  - Scombroidosis
  - Monosodium glutamate (MSG)
- Nonorganic disease
  - Panic attacks
  - Münchhausen's stridor
  - Vocal cord dysfunction syndrome
  - Undifferentiated somatoform anaphylaxis
- Miscellaneous
  - Capillary leak syndrome
  - Red man syndrome (vancomycin)
  - Pseudoanaphylaxis
  - Neurologic (seizure, stroke)
  - Hyperimmunoglobulin E, urticaria syndrome
  - Pheochromocytoma
  - Urticarial vasculitis
  - "Progesterone" anaphylaxis
  - Hereditary angioedema
- Excess endogenous production of histamine syndromes
  - Systemic mastocytosis
  - Urticaria pigmentosa
  - Basophilic leukemia
  - Acute promyelocytic leukemia (tretinoin treatment)
  - Hydatid cyst

A. Disorders involving hypotension

The most common condition confused with anaphylaxis is the vasodepressor reaction (vasovagal syncope). The vasodepressor reaction is characterized by hypotension, pallor, nausea, vomiting, weakness, and sweating. In severe reactions, loss of consciousness can occur. Such reactions are due to a threatening event or emotional trauma. The characteristic bradycardia associated with vasodepressor reactions has been used as a differential diagnostic feature to distinguish them from anaphylaxis. However, this single feature may not be trustworthy and may be insufficient alone to distinguish a vasodepressor reaction from an anaphylactic event. Thus, perhaps the most important distinguishing feature between the two types of events is the absence of cutaneous symptoms (other than sweating) in the vasodepressor response. Characteristically, the skin in patients suffering a vasodepressor response is pale, and there is a "cold sweat."

Other forms of hypotension include hemorrhagic, cardiogenic, and endotoxic shock. The absence of cutaneous features distinguishes these from episodes of anaphylaxis.

B. Disorders involving flushing

Since flushing occurs relatively frequently in anaphylactic episodes, a number of other causes of flushing should be considered. These include carcinoid syndrome; postmenopausal flush; alcohol ingestion; drugs, including niacin; and vasoactive polypeptide–secreting tumors. Flushing may present in a "wet" form and "dry" form. In the wet form, there is associated sweating mediated by sympathetic cholinergic nerves that supply sweat glands in the skin. It is characteristic of postmenopausal flushing and the flush produced by ingestion of capsaicin. The dry form involves direct vasodilatation without stimulation of the sweat glands and produces a dry flush as is seen in the carcinoid syndrome. Other forms of dry flush include those due to niacin, nicotine, catecholamines, and angiotensin-converting enzyme inhibitors. A dry flush can also be seen in vasoactive polypeptide–secreting tumors such as those that occur in the pancreas and other areas of the gastrointestinal tract and with thyroid medullary carcinoma. Dry flushing can also occur due to pheochro-mocytoma, rosacea, hypoglycemia, mastocytosis, and niacin ingestion.

The most common cause of flushing is alcohol-induced flush. It causes a nonelevated intense erythema more frequently distributed across the trunk, neck, and face, occurring minutes after the ingestion of alcohol. Symptoms usually peak 30 to 40 minutes after ingestion and usually subside within 2 hours. There are two forms. One form occurs when alcohol is taken simultaneously with certain drugs and in patients with certain illnesses. Such drugs include griseofulvin, cephalosporins, and niacin. Conditions predisposing to alcohol-induced flush include lymphoreticular neoplasms, the hypereosinophilic syndrome, and mastocytosis. The second form of alcohol-induced flush is due to a deficiency in acetaldehyde dehydrogenase-2. This enzyme metabolizes acetaldehyde, a metabolite of alcohol. In patients with a deficiency of this enzyme, there is accumulation of acetalde-hyde, which results in mast cell degranulation.

A group of "restaurant syndromes" can also cause symptoms similar to anaphylaxis. Perhaps the most common of these, and the one that resembles anaphylaxis to the greatest degree, is scombroidosis. This condition is produced by the ingestion of histamine contained in spoiled fish. Histamine is the major chemical involved in the production of symptoms, but all symptoms are not caused by histamine alone. The ingestion of histamine-contaminated spoiled fish is more toxic than the ingestion of equal amounts of pure histamine; therefore, other chemicals have been incriminated. The most likely is *cis*-Urocanic acid, an imidazole compound similar to hista-mine. *Cis*-Urocanic acid can also cause mast cell degranulation, thus perhaps to some extent augmenting the response. Histamine is produced by histidine-decarboxylating bacteria that cleave histamine from histidine in spoiled fish. This histamine production occurs shortly after the death of the fish and therefore can occur on the fishing vessel, at the processing plant, in the distribution system, or in the restaurant or home. Such contaminated fish cannot be distinguished by their appearance or smell, and cooking does not destroy the histamine. The onset of symptoms in scombroidosis occurs within a few minutes to several hours after the ingestion of fish. Several members eating at the same table may be affected. The episodes usually last a few hours but can persist for days. Symptoms include urticaria, flush, angio-edema, nausea, vomiting, diarrhea, and a fall in blood pressure. Neurologic findings can also occur, and rarely wheezing is present. The most common manifestation is face and neck flush accompanied by a sensation of heat and discomfort. Serum tryptase levels are not elevated in histamine poisoning, whereas plasma histamine and 24-hour urinary histamine metabolites are present

in increased amounts (see below under "Laboratory Tests").

Nonorganic problems that are psychologically based have also been confused with episodes of anaphylaxis. These include panic attacks, globus hystericus, vocal cord dysfunction syndrome, Münchhausen's stridor, and undifferentiated somatoform anaphylaxis. Panic attacks, except for flush and sweating, are usually devoid of cutaneous manifestations but can be characterized by tachycardia, gastrointestinal symptoms, and shortness of breath. There is no pruritus or true airway obstruction, and the absence of urticaria and angioedema is usually a telltale sign. Undifferentiated somato-form anaphylaxis is a term used to describe patients who present with manifestations that mimic anaphylaxis but who lack confirmatory findings and fail to respond to standard therapy. They often have psychological characteristics of other undifferentiated somatoform disorders.

Anaphylaxis can be a result of an underlying disease and not actually due to exposure to an external agent. Such illnesses include systemic masto-cytosis (see above), urticaria pigmentosa, basophilic leukemia, acute promy-elocytic leukemia treated with tretinoin, and hydatid cyst.

A separate set of disorders present with features suggestive of anaphy-laxis but are pathophysiologically distinct. These include hereditary angio-edema, pheochromocytoma, neurologic disorders (such as seizure and stroke), the "red man syndrome" due to vancomycin, and the capillary leak syndrome. For example, patients with hereditary angioedema present with acute swelling and occasionally exhibit an erythematous, serpiginous rash that can resemble urticaria. This rash accompanied by upper airway obstruction can be confused with an anaphylactic episode. The capillary leak syndrome can present with angioedema, gastrointestinal symptoms, shock, and hemoconcentration. Recurrent episodes have mimicked idiopathic anaphylaxis.

VIII. LABORATORY TESTS

While anaphylaxis is a clinical diagnosis, laboratory tests are useful to help confirm a diagnosis of anaphylaxis or to establish a competing diagnosis (Table 13-4).

A. Serum tryptase

By far, the most commonly employed biomarker used to confirm a diagnosis of anaphylaxis is the measurement of total serum tryptase. Tryptase is secreted constitutively in small amounts. The constitutively secreted tryptase is, for the most part, an immature form of tryptase, beta-protryptase. With mast cell degranulation, there is a marked increase in tryptase levels due to the secretion of mature beta-tryptase. Serum levels peak 60 to 90 minutes after the onset of symptoms and usually persist for up to 6 hours. The optimal time for drawing a serum tryptase is between 2 and 3 hours after the onset of symptoms. However, elevated serum tryptase levels have been found as long as 24 hours after symptom onset. Unfortunately, serum tryptase lacks sensitivity but is highly specific. Nonetheless, because of the lack of sensitivity, a normal total tryptase value obtained during an event does not rule out the diagnosis of anaphylaxis. This is especially true for the diagnosis of events due to food allergy.

An elevated serum tryptase obtained during an asymptomatic phase is a reasonably good screening test to identify underlying systemic mastocytosis in a patient who has had an episode of anaphylaxis. Patients with mastocytosis may have elevated levels of baseline total serum tryptase in between episodes. However, it should be noted that mastocytosis

can be present with normal baseline serum tryptase levels. It was originally thought that a baseline level of serum tryptase of 20 ng/mL was necessary to raise suspicion for mastocytosis, but it has been recently shown that levels far lower, as low perhaps as 11 ng/mL, may reflect an underlying increased burden of mast cells. An elevated level above 20 ng/mL is highly specific, but again this test lacks sensitivity, and a normal baseline level does not rule out the presence of mastocytosis.

It should also be remembered that elevated total serum tryptase can occur in myeloproliferative disorders, the hypereosinophilic syndrome associated with FIP1L1/PDGFRA mutations, and in patients with end-stage kidney disease.

B. Plasma histamine

Plasma histamine rises much more rapidly than does serum tryptase. Plasma histamine levels can be elevated 5 to 10 minutes after the onset of symptoms. However, such levels are evanescent, usually returning to normal within 60 minutes after the onset of the event. For this reason, plasma histamine levels are of little help if the patient is seen as long as an hour after the event. In this case, however, a 24-hour urinary collection for histamine metabolites may be useful. Such metabolites can be elevated for as long as 24 hours. Unfortunately, there are disparities between histamine and tryptase levels. If the patient is seen soon enough, plasma histamine levels may be more sensitive and may also correlate better with clinical manifestations. Plasma histamine may be more likely to correlate with cutaneous manifestations as well as wheeze.

C. Other tests

The majority of patients suffering from mastocytosis have a point mutation in the c-kit receptor (816V). A test for 816V on blood is now available. However, its exact sensitivity and specificity has not been established, and it appears to be less sensitive than the same test performed on the bone marrow. Serum serotonin and urinary-5 hydroxyindoleacetic acid can be measured if one is considering flushing due to the carcinoid syndrome. The measurement of various gastrointestinal vasopeptides is available. These include substance P, neurokinins, vasointestinal poly-peptide, pancreastatin, and others. These measurements may be useful to rule out the presence of a vasoactive peptide secreting tumor. Octreotide-assisted CT scanning is also useful in this regard. Plasma-free metanephrine and urinary vanilmandelic acid are employed if one is considering a paradoxical response to a pheochromocytoma.

Table 13-4 Laboratory Tests for Evaluation of Anaphylaxis

Test	Comment
Serum tryptase	Serum tryptase levels usually peak 60–90 min after the onset of symptoms and persist 6 h. However, tryptase levels can be elevated for as long as 24 h. Nonetheless, ideally, measurement should be obtained between 1 and 2 h after onset of symptoms.
Plasma histamine	Plasma histamine levels rise earlier than tryptase levels, increasing within 5–10 min after the onset of symptoms. Levels are elevated only evanescently and usually return to normal after 60 min. Thus, they are of little help if the patient is seen more than an hour after the event began.
24-h urinary histamine metabolites (N-methylhistamine)	Urinary histamine metabolites can be elevated for up to 24 h after the onset of the event.
Serum serotonin and urinary 5-hydroxyindoleacetic acid	Used to rule out carcinoid syndrome
Gastrointestinal vasopeptides including pancreastatin, vasointestinal polypeptide, substance P, neurokinin, and others	Useful to rule out the presence of a vasoactive polypeptide that can be associated with pancreatic or small bowel tumors and medullary carcinoma of the thyroid
Plasma-free metanephrine and urinary vanilmandelic acid	Useful to rule out a paradoxical pheochromocytoma
Octreotide-enhanced CT of abdomen	If elevated levels of vasopeptides are noted, may be helpful in locating site of synthesis (e.g., pancreatic or small bowel tumor)

IX. MANAGEMENT

A. Approach to the patient with anaphylaxis following the event

An algorithm outlining the approach to a patient who has experienced an anaphylactic episode and is seen after the event is found in Figure 13-1. In evaluating a patient who has experienced a possible previous episode of anaphylaxis, the most important procedure is the history. A detailed history should be obtained, which includes elements such as establishing the time of the occurrence of the attack, the setting in which the attack occurred, the treatment that was required, whether or not an emergency room visit was necessary, and the duration of the episode. The history should include a detailed list of ingestants, including medications, consumed within 6 hours of the event; any history of sting or bite; whether or not exercise or sexual activity occurred prior to during the event; and whether or not there was exposure to heat or cold prior to or during the event. The symptoms of course should be reviewed in detail, and it should be determined as to whether or not the event was biphasic in nature.

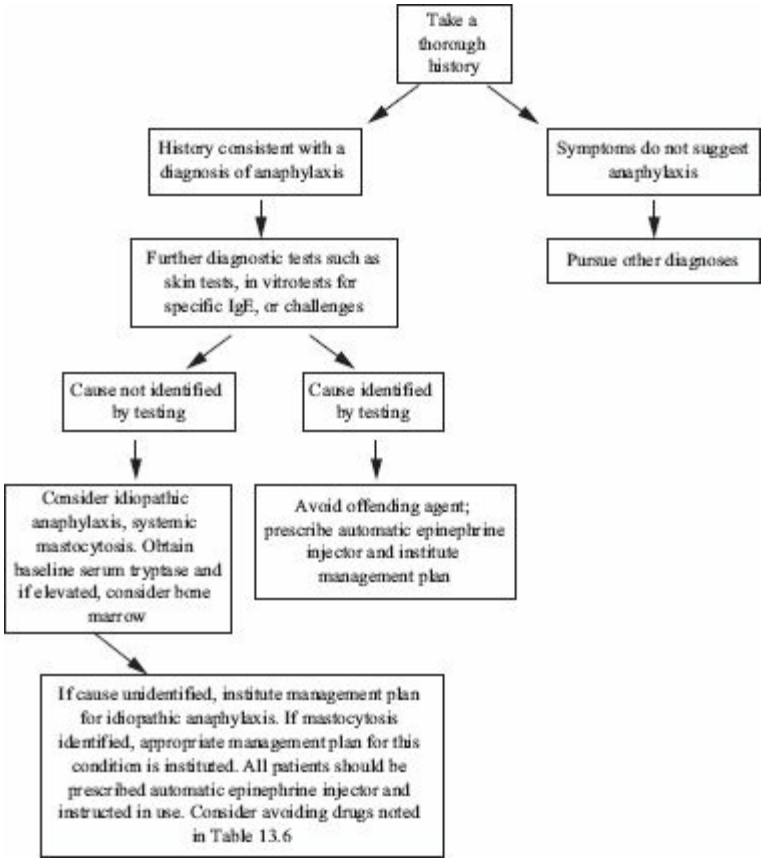

Figure 13-1. Algorithm for the evaluation of a patient who has experienced an anaphylactic episode.

B. Prevention

Measures for the prevention of anaphylactic episodes are noted in Table 13-5. If a drug was responsible for an episode of anaphylaxis, the drug allergy history should be recorded in a prominent and consistent place in the medical chart. Proper interpretation of this history requires a knowledge of cross-reacting agents. The patient should be instructed to avoid all agents that might present a risk. When a drug allergy is present, a substitute, non–cross-reactive agent should be administered. Some patients require the readministration of drugs that have produced an event. In such instances, pharmacologic pretreatment, provocative challenge dosing, or desensitiza-tion can be utilized. In addition, anaphylactic episodes are usually worse when allergens are given by injection rather than orally, and therefore, oral administration of drugs should be used whenever possible. If an injection is given in the office, the patient should remain on-site 20 to 30 minutes for observation. Finally, consideration should be given to discontinuation of drugs, which might complicate therapy or increase the severity of a future episode (Table 13-6).

Table 13-5 Strategies to Prevent Anaphylaxis and Anaphylactic Deaths

General Measures For the Population as a Whole

1. Obtain thorough history.
2. Record drug history in dedicated and prominent portion of chart.
3. Administer drugs orally rather than parenterally when possible.
4. Check all drugs for proper labeling.
5. Patients to remain 30 min in office after administration of in-office drugs, especially injections

For Patients at Risk

A. Be aware of immunologic and biochemical cross-reactivity between drugs, and avoid those that may produce events (e.g., all NSAIDs in the aspirin-sensitive asthmatic, all beta-lactam drugs possible in the penicillin-sensitive patient).
B. For patients with food allergy, give instructions in label reading and avoidance of potentially cross-reacting foods (e.g., avoidance of all crustaceans in lobster-sensitive patient).
C. Have patients wear and carry warning identification labels (e.g., Medic Alert).
D. Teach self-injection of epinephrine.
E. Emphasize the need to keep automatic epinephrine injectors available at all times.
F. Consider discontinuing where possible drugs that may interfere with therapy or potentially worsen an event (e.g., beta-adrenergic blocking agents, angiotensin-converting enzyme inhibitors, angiotensin II blockers, monoamine oxidase inhibitors, and possibly certain tricyclic antidepressants).
G. Employ when indicated special procedures such as desensitization, pharmacologic pretreatment, and provocative challenge.

Table 13-6 Drugs That May Increase the Risk of Anaphylaxis, Increase the Severity of an Attack, or Complicate Therapy

Drug	Potential Adverse Effect
Beta-adrenergic blocking agents	Can diminish the effect of epinephrine used to treat an event. Can potentially make the event worse by preventing the response to endogenously secreted epinephrine and norepinephrine. While blocking the beta-adrenergic effect of epinephrine, may enhance the alpha-adrenergic effect inordinately.
Angiotensin-converting enzyme inhibitors	May prevent the effect of the compensatory secreted angiotensin-converting enzyme, thus worsening hypotension. Also prevent the degradation of bradykinin. Excessive bradykinin activity has been shown to occur during anaphylactic episodes. Has been shown to increase the risk of reactions to venom immunotherapy and perhaps the severity of events due to hymenoptera stings.
ACE blockers	Only theoretical risk. Prevent activity of angiotensin II.
Monoamine oxidase inhibitors	Complicate therapy because they prevent degradation of epinephrine used to treat an event, thus making the proper dose more difficult to assess
Tricyclic antihistamines	Prevent reuptake of catecholamines and thus can exaggerate effect of epinephrine. This makes the proper dose more difficult to assess.

All patients who are at risk for anaphylaxis should wear identifying medical jewelry (e.g., Medic Alert Foundation, 2323 Colorado Ave, Turlock, California 95382). All such patients should be instructed in the use of an automatic epinephrine injector and encouraged to have the injector available at all times. They should also be reminded to refill it upon its expiration.

C. Treatment of the acute event

An algorithm outlining the management steps for anaphylaxis is shown in Figure 13-2. The management of an anaphylactic episode requires that appropriate equipment and medications be available, which is shown in Table 13-7.

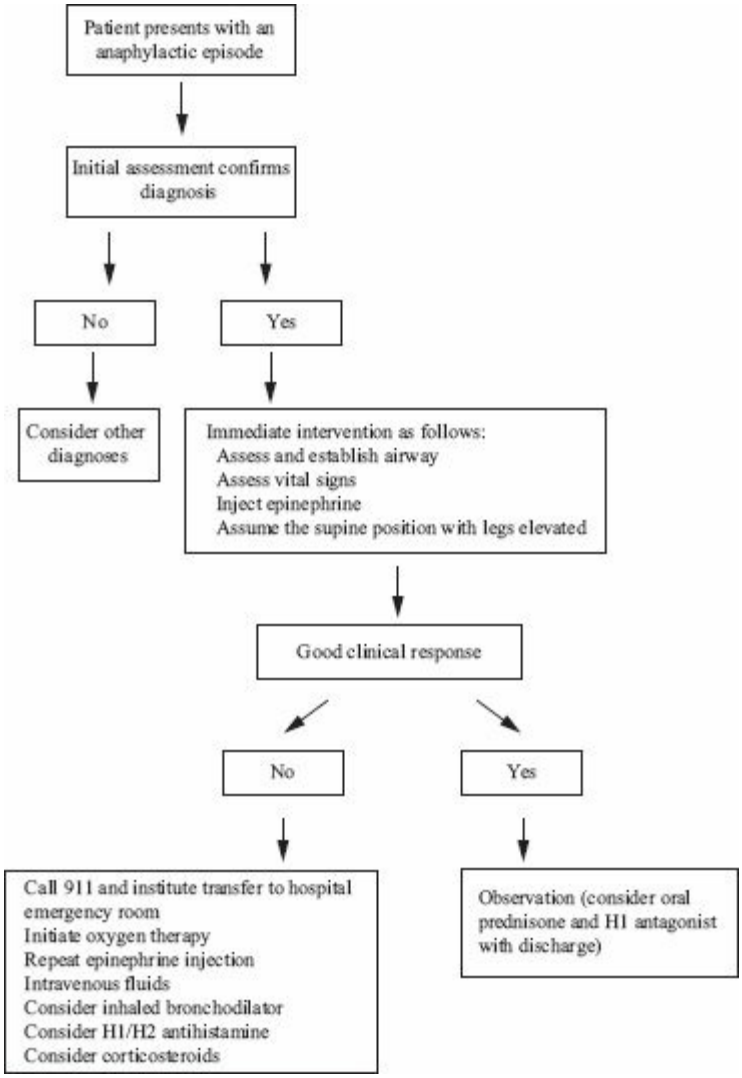

Figure 13-2. Algorithm outlining the management of the acute event.

Table 13-7 Suggested Office Equipment for Management of an Anaphylactic Episode

- Oxygen delivery
  - Canister nasal O_2
  - Face mask
  - Tubing
  - Nasal probe
- Intravenous supplies
  - Normal saline
  - 5% dextrose
  - Connection tubing and needles
- Medications
  - Epinephrine
  - Diphenhydramine
  - Consider H2 agent such as ranitidine, cimetidine
- Systemic corticosteroids
  - Prednisone
  - Hydrocortisone for intravenous injection
- Consider other agents
  - Glucagon
  - Atropine for injection
  - Albuterol inhalation solution with compressor nebulizer
  - Dopamine or norepinephrine for intravenous infusion
  - Consider defibrillator

The acute management of an anaphylactic event requires immediate recognition and institution of therapy. Initial management is directed to the preservation of the airway and assessment of vital signs. Establishment of the airway should be done immediately while assessing the vital signs and placing the patient in the recumbent position with legs elevated. Simultaneously, epinephrine should be administered. Injection in the vastus lateralis muscle (lateral thigh) produces a more rapid rise in blood epinephrine levels and, because of this desirable effect, has been suggested as the initial route of administration of choice. The dose in an adult is 0.3 to 0.5 mg. The dose in a child is dependent on weight (0.01 mg/kg). Once this has been done, further therapy depends on the assessment. It should be emphasized, however, that epinephrine therapy is essential and is the initial drug of choice. There is evidence to suggest that a delay in epinephrine administration can be a risk factor for a fatal event as well as for a biphasic event. Therefore, this drug should be administered as soon as the diagnosis has been established.

If the patient responds to the initial treatment with an epinephrine injection, he or she should be observed for recurrences, and if the patient remains asymptomatic, he or she can be discharged from the clinic. The exact time for observation after an attack responding to a single dose of epinephrine has not been established. However, as noted above, the majority of recurrent reactions will occur within 8 hours. How long would one keep the patient under observation after an event occurring in-office remains a matter of clinical judgment. It would be prudent, however, to observe the patient, if possible, for a minimum of 2 hours. Consideration can be given to treating them with an H1 antagonist either intramuscularly or by mouth subsequent to epinephrine administration and a short course of prednisone upon discharge. However, there is no substantive documentation that additional therapy will prevent a recurrence of symptoms or alter the outcome of successful treatment with an initial dose of epinephrine.

If the episode does not respond to a single dose of epinephrine, other therapies should be considered, and a 911 call should be placed. If there is no response within 5 to 10 minutes, a second dose of epinephrine should be administered, and a third if no response in another 5 to 10 minutes. At

that time, consideration for supplemental therapy such as an inhaled bronchodilator, an H1/H2 antagonist, and intravenous fluids should also be considered, depending on the patient's symptoms. For example, an inhaled bronchodilator would be the drug of choice if the persistent symptoms were shortness of breath and wheeze. If hypotension was present, intravenous fluids should be given. The rate of administration of fluid is titrated against the blood pressure response. In severe cases, as much as a liter in an hour can be administered. If cutaneous manifestations were present, an H1/H2 antihistamine should be considered (Table 13-8). If the patient is taking a beta-adrenergic blocker and hypotension persists, in addition to fluids, glucagon may be employed (Table 13-8). For hypotension not responding to fluid administration, vasopressors such as norepinephrine or dopamine can be employed (Table 13-8).

Table 13-8 Drugs Used to Treat Anaphylaxis

Drug	Dose and Route of Administration	Comment
Epinephrine	1:1,000 0.3–0.5 mL IM lateral thigh (adult) 1:1,000 0.01 mg/kg or 0.1–0.3 mL IM lateral thigh (child) 0.1–1.0 mL of 1:1,000 aqueous epinephrine diluted in 10 mL normal saline IV (see text for details)	Initial drug of choice for all episodes; should be given immediately; may repeat q 5–15 min If no response to IM administration and patient in shock with cardiovascular collapse, can consider intravenous administration
Antihistamines		
Diphenhydramine	25–50 mg IM or IV (adult) 12.5–25 mg PO, IM, or IV (child)	Route of administration depends on severity of episode. Also consider oral administration when discharged from office after response to therapy with epinephrine when antihistamine not given for acute episode.
Ranitidine	4 mg/kg IV cimetidine	
Cimetidine	1 mg/kg IV ranitidine	
Corticosteroids		
Hydrocortisone	100 mg–1 g IV or IM (adult) 10–100 mg IV (child)	Exact dose not established; other preparations such as methylprednisolone can be used as well; for milder episodes, prednisone 30–60 mg may be given. Also consider oral administration when discharged from office after response to therapy with epinephrine. No established dose, but prednisone 50 mg in adult and 30 mg in child down to age 6 y suggested.
Albuterol inhalation for resistant bronchospasm	Dose as for asthma (0.25–0.5 mL in 1.5–2 mL saline q4 h, prn)	Useful for bronchospasm not responding to epinephrine

Intravenous fluids (normal saline or Ringer's lactate)	1,000–2,000 mL rapidly in adults 30 mL/kg in first hour in children 500 mL rapidly followed by slow infusion in adults	Rate of administration titrated against blood pressure response
Vasopressors Dopamine	400 mg in 500 mL; dextrose 5% in water as IV infusion; 2–20 µg/kg/min	The rate of infusion should be titrated against the blood pressure response; continued infusion requires intensive care monitoring.
Drugs employed in patients who are beta-blocked		
Atropine sulfate	0.3–0.5 mg IV; may repeat every 10 min to a maximum of 2 mg in adults	Glucagon is probably the drug of choice with atropine useful only for treatment of bradycardia.
Glucagon Ipratropium	Initial dose of 1–5 mg IV followed by infusion of 5–15 µg/min titrated against blood pressure	Ipratropium might be considered as an alternative or added to inhaled beta-adrenergics for wheezing.

Traditionally, corticosteroids have been used to treat anaphylactic episodes. There is no strong evidence to support that they alter outcomes except for some evidence that they may have a role in diminishing the frequency of late phase or recurrent responses. As mentioned, an oral dose of prednisone can be considered upon discharge of a patient treated with a mild episode, and, in addition, intravenous corticosteroids can be considered for the therapy of a more severe case. As mentioned, if any therapy beyond one injection of epinephrine is necessary, an immediate 911 call is indicated, and the patient should be transported to a hospital facility for further treatment. In more severe cases, a more prolonged observation time after cessation of symptoms is also prudent. A minimum of 8 hours, and in some cases 24 hours, of observation is recommended.

The use of a tourniquet proximal to the injection site to slow absorption of antigen has been suggested for patients experiencing a reaction due to antigen administered in the limb. It is debatable as to whether or not this is an effective measure. Should it be used, the tourniquet should be loosened every few minutes to prevent anoxic injury. It has been suggested that epinephrine should also be injected into the site where allergen was injected to slow the absorption of antigen. The suggested dose has ranged from 0.1 to 0.2 mg (in addition to the dose mentioned above administered to treat the acute event). As with a tourniquet, there is no evidence that injection of epinephrine into the site alters outcomes. For this reason, we do not usually employ a tourniquet in treating anaphylactic episodes.

14

Insect Allergy

David B. K. Golden

Insect bites and stings usually cause relatively mild, transient local inflammation. In sensitized individuals, allergic reactions may result in more severe local reactions as well as generalized systemic symptoms ranging from mild to fatal responses. Acute anaphylactic reactions can be abrupt in onset and are considered true medical emergencies. In the United States, almost 9 million people have had previous systemic reactions to stings, and as many as 50 million people are sensitized to insect venoms and have a risk of allergic reactions. Although anaphylaxis has been reported in a small number of cases from biting insects, it is the stinging insects that cause most systemic reactions and these will be the focus of this chapter.

STINGING INSECT ALLERGY

I. CLINICAL MANIFESTATIONS

A. Normal reactions to insect bites and stings generally cause localized itching, pain, burning, redness, and mild swelling. This normal reaction is caused by several components in the saliva (bites) or venom (stings) of the insects, including enzymatically active proteins and vasoactive amines (e.g., hista-mine and kinins). The reaction usually subsides in hours, although some individuals with sensitive skin describe more intense local reactions lasting several days.

B. Large local reactions are usually late-phase allergic reactions causing severe swelling contiguous with the site of the sting; swelling distant from the site of the sting would be a sign of systemic reaction with angioedema. The abnormal swelling often begins more than 6 hours after the sting, enlarging for 24 to 48 hours and resolving slowly over an additional 2 to 7 days. Such large local reactions cause induration and tense edema larger than 8 cm in diameter and can involve an entire limb. The intense local inflammation may cause the appearance of lymphangitic streaks toward the inguinal or axillary nodes, but this should not be mistaken for cellulitis when it appears in the first 24 to 48 hours. Infection at the site of the sting is quite uncommon and takes more than 48 hours to develop. Large local reactions are not usually dangerous, but in the head and neck area, they could cause delayed localized compression of the airway, especially in the case of a sting on the tongue or pharynx.

C. Systemic reactions may cause any one or more of the signs and symptoms of anaphylaxis. Cutaneous signs occur in more than 80% of all cases and are the only manifestation of the reaction in 15% of adults. Airway symptoms (throat tightness, dyspnea, cough, wheezing) are reported by 50% to 60% of adults and children, and circulatory symptoms (dizziness, syncope, hypotension, unconsciousness) occur in 30% of adults. Children have a higher frequency of isolated cutaneous reactions (60% of cases) and a lower frequency of vascular symptoms and anaphylactic shock (5%) compared to adults. Systemic reactions can become progressively more severe with each sting in some cases but usually follow a more

predictable and individual pattern in each patient. Anaphylaxis can be protracted or biphasic in more than 20% of cases of severe (grade 3 or 4) systemic reactions, so medical observation is recommended for 6 hours. Occasionally, individuals are resistant to epinephrine, especially those taking a beta-blocker medication. Patients discharged from emergency care of anaphylaxis must receive instructions on the need for an epinephrine autoinjector device, an allergy consultation, and preventative treatment. It should be explained to all patients that self-administered epinephrine is not a substitute for emergency medical attention.

D. Toxic reactions have occurred after multiple stings, and very large numbers (in the hundreds) can be fatal (e.g., Africanized honeybees). Other unusual patterns of reactions have been reported including nephropathy, central and peripheral neurologic syndromes, idiopathic thrombocytopenic purpura, and rhabdomyolysis, but these responses are not immunoglobulin E (IgE) mediated. Serum sickness reactions to stings are infrequent but have been related to venom-specific IgE antibodies. There are also reports of allergic sting reactions being followed by months of chronic urticaria or cold urticaria.

II. INSECT ANTIGENS

The most common insects causing systemic allergic reactions are of the order Hymenoptera (Table 14-1). There are three Hymenoptera families of importance: Bees (honeybees, bumblebees) and vespids (yellow jackets, hornets, wasps) are best known. Fire ants (*Solenopsis* sp.) have become a rapidly increasing public health hazard in the southeast and south central United States, particularly on the Gulf Coast.

Table 14-1 Characteristics of Common Stinging Insects (Hymenoptera)[a]

Insect type	Appearance	Habitats	Sting Characteristics	Venom Constituents
Honeybee	Hairy bodies with yellow and black markings	Domestic hives, hollow trees, caves (rural and suburban)	Barbed stinger; only insect to always leave stinger; stings only if provoked	Hyaluronidase, phospholipase A, histamine, lecithinase; smooth muscle contractor
Wasp	Hairless body with narrow waist, black or brown markings	Window frames, eaves of houses, wood railings, trees, shrubs, (rural and suburban)	Occasionally contaminated	Histamine, serotonin, hyaluronidase, lecithinase
Hornet	Short waist, truncated body, with sparse hair, dark band under eyes	Oval nests in trees and bushes (rural and suburban)	Occasionally contaminated	Histamine, serotonin, kinins, acetylcholine
Yellow jacket	Similar to hornet, with black and bright yellow markings but no dark band	Large nests in ground and walls (rural and suburban)	Often contaminated, aggressive, most common culprit in most areas, may leave stinger	Histamine, serotonin, kinins
Imported fire ant	Appearance of domestic ants but with well-developed posterior stinging apparatus	Nests in ground, primarily in Gulf Coast states (rural and suburban)	Bites and stings; produces multiple pustules for 3–8 d, with pain and burning	Cytotoxic and hemolytic alkaloids

[a] Generally, patients with honeybee sensitivity are not reactive to wasps, hornets, and yellow jackets. There is a 50% incidence of cross-reactivity between wasps and hornets or yellow jackets.

For 50 years, whole-body extracts were used for skin testing and immunotherapy, because it was believed that allergic sensitivity was related to an "intrinsic bee protein" present in the whole insect body as well as the venom. In the 1970s it was established that whole-body extract tests and treatment were no more effective than placebo (except for fire ants), whereas

immunotherapy utilizing purified venom effectively prevented anaphylaxis in 80% to 98% of patients (depending on the species). Honeybee venom is immunochemically distinct, and the primary allergen is phospholipase A. Africanized honeybees ("killer bees") do not differ from other honeybees in the quantity or quality of the venom, but they have a great tendency to swarm and attack, thus causing life-threatening or fatal toxic reactions when they sting in the hundreds. The vespid venoms have a high degree of cross-reactivity, and the same primary allergen, "antigen 5," is present in yellow jacket and hornet venoms. *Polistes* wasps are more distantly related to the other vespids, and only 50% of yellow jacket–allergic patients have positive tests to wasp venom related to the cross-reactivity of the major allergen. Fire ant venoms are quite different in that they contain very little protein in an unusual suspension of alkaloid toxins that cause the characteristic painful vesicular eruption. The allergenic proteins in fire ant venoms are unique, except for one that shows limited cross-reactivity with vespid allergens. The diagnostic and therapeutic materials currently supplied by commercial laboratories are fire ant whole-body extracts, but unlike the situation with the other Hymenoptera, these fire ant extracts show reasonable allergenic activity for diagnostic skin testing and for preventive immunotherapy (but with no placebo-controlled studies).

III. EPIDEMIOLOGY AND NATURAL HISTORY OF REACTIONS

A. Large local reactions occur with uncertain frequency but are estimated to affect 10% of adults, possibly because the size of the reaction is subject to exaggeration. Most patients (60% to 80%) with large local reactions have positive venom skin tests, but the natural history of large local reactions in children and adults suggests a 4% to 10% frequency of systemic reactions to subsequent stings.

B. Systemic reactions to insect stings can develop at any age, often following a number of uneventful stings. Systemic allergic reactions have been reported to occur in approximately 3% of adults and 1% of children. At least 50 fatal sting reactions occur each year in the United States, and many other sting fatalities are believed to go unrecognized. In cases of unexplained sudden death in the summer, postmortem blood samples often show the presence of venom-specific IgE antibodies as well as an elevated level of serum tryptase, strongly suggesting the possibility of fatal insect sting anaphylaxis.

The risk of anaphylaxis to a subsequent sting varies according to the history and skin tests. The highest risk (60% to 70%) is in patients who have had recent and severe reactions. The chance of another systemic reaction never disappears but declines slightly over time. Some studies suggest that the risk is as low as 25% after 10 years, while other studies find no correlation between the chance of sting reaction and the time since the last reaction. The risk of anaphylaxis can persist for decades even with no intervening stings. The lowest risk is in children with isolated cutaneous systemic reactions (generalized urticaria and/or cutaneous angioedema), who have <15% risk of urticaria and <3% risk of anaphylaxis to subsequent stings.

C. IgE antibodies to Hymenoptera venoms are frequently found in the adult population. More than 20% of normal adults have positive skin tests or serologic tests for IgE antibodies to yellow jacket or honeybee venom, and these patients invariably report prior stings but very few report abnormal reactions to those stings. Half of those with positive tests became negative after a few years, but more than 15% of those who were later stung had a systemic reaction. In untreated

patients with systemic reactions to stings, venom skin tests may gradually become weaker over time but do not usually become negative during 5 to 10 years of follow-up. In patients receiving venom immunotherapy (VIT), venom-specific IgE increases in the first few months of initial therapy, returns to baseline after 1 year, and then declines steadily with time (even after an intercurrent sting or after venom therapy is discontinued). After 6 and 10 years of VIT, these patients become skin test negative in approximately 25% and 67% of cases, respectively.

D. Children have an estimated prevalence of systemic reactions to stings of at least 0.4% to 0.8%. The notion that children routinely outgrow insect sting allergy is probably due to the large number of children with isolated urticaria after a sting. In children with strictly cutaneous systemic reactions, the risk of anaphylaxis after a subsequent sting is <3%. However, children with histories of moderate or severe reactions who did not receive VIT experienced systemic reactions in 25% to 40% of cases when they were stung up to 20 years later. Children who received VIT had a much lower risk of developing systemic reactions even 10 or more years after stopping treatment.

IV. DIAGNOSIS

A. History

The patient's history of the reaction is most important in establishing a diagnosis of insect allergy. A thorough inquiry should include all of the details regarding the circumstances and location of the sting event, the number and location of the stings, the type of insect(s), the time course of the reaction, a description of the pattern and severity of all associated symptoms and signs, and the response to any treatment that was administered. The history should also include any previous stings that have occurred (especially in recent months), any atopic conditions, and all medications that were taken at the time of the sting. It may be difficult to distinguish historically between a large local swelling and angioedema and between lightheadedness or dyspnea and anxiety or hyperventilation. It is also advisable to ask specifically about prior sting reactions during periodic health maintenance visits, because many patients will not volunteer this information.

B. Venom skin tests

1. **Indications.** Venom skin tests are best performed by specialists (e.g., allergist/immunologist) experienced with the technique and interpretation of the tests. Venom skin tests are recommended in patients with a history of systemic reaction to a sting but not necessarily in those with large local reactions or in children with isolated diffuse urticaria.
2. **Testing materials and preparation.** Commercial venom protein extracts are purified preparations of Hymenoptera venoms that have been standardized in order to maintain a consistent and reproducible response during skin testing and immunotherapy. There are five venoms available for testing: honeybee, yellow jacket, yellow hornet, white-faced hornet, and wasp venom. These products are supplied as lyophilized preparations and must be reconstituted with a special diluent containing 0.9% saline, 0.03% human serum albumin (HSA) (which stabilizes venom proteins and prevents their adsorption to the walls of the container), and 0.4% phenol. After reconstitution, the full-strength venom extract is diluted in a serial fashion to achieve the concentrations required for skin testing.

Of note, the manufacturer's instructions concerning the storage of the lyophilized materials (do not freeze) and storage times before expiration should always be observed.

Whole-body extracts of Hymenoptera insects do not contain enough venom proteins for either accurate diagnosis or therapy of insect sting allergy. An important exception is the case of fire ant sensitivity, which can be tested and treated using whole-body fire ant extracts.

3. **Methods.** The standard method for venom skin testing is the intradermal technique, beginning with an appropriately low concentration (0.001 mg/mL),and then increasing until a positive result is obtained or the highest concentration is achieved (1 mg/mL). Patients with a history of severe systemic reactions should be tested initially with a puncture technique using a venom concentration between 1 and 100 mg/mL before proceeding to the intradermal technique.

   Sensitization to multiple venoms may be present even when there has only been a reaction to a single insect. Therefore, skin testing should be performed with a complete set of the five Hymenoptera venoms, a negative diluent (HSA–saline) control, and a positive histamine control. The preferred location for performing venom skin tests is on the flexor surface of the forearm.

4. **Interpretation of venom skin tests** is based upon the size of the wheal and erythema and the presence of pseudopodia. Table 14-2 summarizes the recommended guidelines for skin test interpretation provided by major manufacturers. Reactions of 1+ or greater (larger than the negative control) at a concentration of 1 µg/mL or less of venom indicate the patient is venom sensitive. The positive venom skin test confirms the allergic nature of the sting reaction and identifies the causative insect.

Table 14-2 Interpretation of Venom Skin Test Responses

	Mean Diameters (cm)	
Grade	Wheal	Erythema
0	<0.5	<0.5
±	0.5–1.0	0.5–1.0
1+	0.5–1.0	1.1–2.0
2+	0.5–1.0	2.1–3.0
3+	1.0–1.5; pseudopodia	3.1–4.0
4+	>1.5; many pseudopodia	>4.0

Skin test results in patients with a convincing history are usually clearly positive but can be negative in up to 30% of patients. There are three situations in which skin tests may be negative: (i) in a patient with a strongly positive history in whom the sting has occurred in the remote past and may represent a loss of sensitivity; (ii) during the refractory ("anergic") period for up to 6 weeks after a sting reaction. It is reasonable to perform skin tests during this period if there is a seasonal need to begin immunotherapy as soon as possible. However, if the results are negative, the tests should be repeated in 4 to 6 weeks; and (iii) in some cases of sting anaphylaxis that have been said to be non-IgE mediated and may be related to subclinical mastocytosis or simply "toxic" mast cell hyperreleasability. There are reports of patients with sting reactions who had negative skin tests and experienced systemic reactions to subsequent stings. Most of these patients had a positive serum venom-specific IgE test, which suggests the importance of performing a serologic

test for venom-specific IgE antibodies in patients with a positive history and negative skin test. There is unexplained variability in the expression of venom skin tests such that a relatively low level of sensitivity may show as a positive skin test on one occasion but negative weeks or months later.

There are many different patterns of venom skin test sensitivity. Skin tests are positive to all three of the common vespid skin test preparations (yellow jacket, yellow hornet, white-faced hornet) in 95% of ves-pid allergic patients. Notably, the degree of skin test sensitivity does not correlate reliably with the degree of sting reaction. The strongest skin tests often occur in patients who have had only large local reactions and have a very low risk of anaphylaxis, whereas some patients who have had abrupt and near-fatal anaphylactic shock show only weak skin test (or serologic) sensitivity. In fact, almost 25% of patients presenting due to systemic allergic reactions to stings were skin test positive only at the 1.0 μg/mL concentration, demonstrating the importance of skin testing with the full diagnostic range of concentrations.

C. Serum venom-specific IgE antibody tests

The diagnosis of insect sting allergy by detection of allergen-specific IgE antibodies in serum (typically by a fluorescent enzyme immunoassay such as the ImmuniCAP test) is a method of high potential but variable performance. In commercial clinical laboratories, the test is sometimes qualitative or poorly standardized and is negative in 10% to 20% of skin test–positive sting-allergic patients. As noted above, however, the serum IgE test may be positive in some patients who have negative venom skin tests. When it is clearly elevated, the serum IgE test result is diagnostic of insect sting allergy and may be used as grounds for starting VIT (in conjunction with a confirmatory history). Serum IgE tests may also be used as an immunologic method for following patients on VIT to document possible changes in sensitivity.

D. Sting challenge

Because many patients with a positive history and skin tests do not react to subsequent stings, some European researchers have recommended that a deliberate sting challenge with a live insect should be performed as the diagnostic procedure of choice to determine the need for immunotherapy. Because of the risks and costs required by sting challenges, most allergists/ immunologists have judged this approach to be both unethical and impractical. Furthermore, sting challenge is not an accurate indicator of future risk of reaction, because patients with negative sting challenges experienced a 20% reaction rate following a second sting. This suggests that reactions following stings are not completely reproducible and depend upon multiple variables involving both the patient and the insect. Sting challenge is primarily useful as a research tool to investigate the allergic response to stings in relation to other variables and treatments.

E. Serum tryptase

Tryptase is one of the mediators released by mast cells during allergic reactions and is more easily measured than histamine using a routine immunoassay. Measurement of tryptase during an acute anaphylactic reaction can serve to confirm that the cause of the observed symptoms is due to allergic mast cell mediator release. Tryptase is also released by mast cells that are abnormal in quantity or activation status. Elevated baseline serum

tryptase (not during a reaction) occurs in patients with mastocytosis or mast cell activation syndromes. Insect sting anaphylaxis is the most common presenting type of mastocytosis-related anaphylaxis. Mastocytosis occurs in 2% to 5% of patients with insect sting allergy, but elevated baseline serum tryptase is found in 5% to 25% of patients with insect sting allergy, especially in relation to hypotension. In patients with moderate to severe sting anaphylaxis, it is important to measure baseline serum tryptase for several reasons: to identify patients with potential mast cell disorders and because such patients must be managed more cautiously due to a significantly higher frequency of reactions to VIT, failure of VIT, and relapse after stopping VIT (including death).

V. TREATMENT

A. Acute reactions

1. Local reactions should be treated symptomatically, with initial cleansing and then ice or cold compresses for several hours after the sting. Oral antihistamines can help reduce the itching and local discomfort, as can a topical steroid cream or ointment. The late-phase allergic inflammatory (large local) reaction may require a brief course of oral corticosteroid (in adults, prednisone 40 to 60 mg initially and then reduced by 10 mg each day for 4 to 6 days). Local infection is uncommon and may occur many days after the sting, often because of excoriation. Severe local allergic reactions may show lymphangitic streaks toward the axillary or inguinal nodes, but this response is inflammatory in nature and not infectious and does not indicate cellulitis when it presents within 2 days of the sting.
2. Systemic reactions should be treated in the same fashion as anaphylaxis due to any cause (see Chapter 10). Epinephrine injection is always the treatment of choice for acute anaphylaxis. Intramuscular injection of epinephrine in the anterolateral thigh (in children 0.01 mg/kg, up to 0.3 mg total dose; 0.3 to 0.5 mg in adults) provides more rapid and more complete absorption than subcutaneous injection in the arm. Additional treatment is often necessary with intravenous fluids, oxygen, and other medications. Patients with anaphylaxis should be observed for 3 to 6 hours because 20% or more may develop delayed, prolonged, or biphasic anaphylaxis; the chance of such reactions is directly related to the severity of the early-phase reaction.

B. Prophylaxis

1. **Avoidance measures.** Patients who have had allergic reactions to stings should be counseled regarding basic avoidance measures, including avoidance of high-risk factors such as eating or drinking outdoors, drinking from a can or straw, outdoor areas where there are food or trash receptacles, walking barefoot outdoors, gardening and yard work, and use of fragrances (see Table 14-3). Insect repellants do not seem to deter stinging insects.

Table 14-3 Patient Information to Limit the Risk of Insect Stings

Avoid drinking outdoors from cans or straws that may harbor stinging insects.
Exercise caution when doing yard work, handling garbage, picnicking, swimming, bicycling, riding in open-air vehicles, boating, camping, or other outdoor activity.
Always wear shoes outdoors.
Avoid loose-fitting clothing that may entrap insects. Insects are attracted to bright colors and floral patterns. Wear light-colored clothing: white, green, tan, and khaki.
Avoid scented perfumes, lotions, soaps, colognes, or hair preparations.
Look for insects in vehicles before driving, and keep vehicle windows closed.
Avoid rapid or jerking movement around insects. Remain still. Most insects will not sting unless provoked.
All nests or hives in the vicinity of the home should be removed by a professional exterminator and not by the insect-sensitive patient.
Insect repellents do not deter stinging insects. Immunotherapy does not lessen the need for other measures of prevention.
Wear an identification tag or bracelet at all times.
Have an epinephrine injection kit available at all times, especially if at greater risk. Instruct family members and companions in its use.
Seek medical attention immediately after emergency treatment is given.

2. Epinephrine for self-injection is a very important element in preparedness for potential episodes of anaphylaxis. Current recommendations are for patients to have immediate access to 2 doses of epinephrine to treat anaphylaxis, because many reactions require more than 1 dose. Preloaded autoinjectors are available commercially as the EpiPen and EpiPen Jr. (Dey Laboratories, Napa, CA), the Twinject, and the Adrenaclick (each in 0.15 or 0.3 mg) (Shionogi Pharma, Atlanta, GA). Patients need careful instruction and demonstration of the correct and safe use of the injector, when to use it (or not use it), and how to check for expiration or deterioration of the medication. Epinephrine injectors should be prescribed (if appropriate instructions are given) for patients who have had previous systemic reactions and possibly for some patients who have had large local allergic reactions.

3. Allergy/immunology consultation is strongly recommended for patients who have had allergic reactions to stings. Those with systemic reactions will require detailed review of their history along with testing for venom sensitivity. Both systemic reactors and large local reactors will require lengthy discussion and counseling on the relative risk of reaction and, when necessary, strategies for avoidance, signs and symptoms to watch for, how to be prepared, prescription and instructions for use of epinephrine, and discussion of the indications, benefits, and risks of VIT.

4. Venom immunotherapy

a. Indications for VIT require a history of previous systemic allergic reaction to a sting and evidence of venom-specific IgE antibodies by skin test or serologic test (see Section IV). In adults and children with large local reactions, and children with strictly cutaneous systemic reactions, VIT is not required. However, some patients will still request treatment because of their fear of reaction and the impact upon their lifestyle and/or frequent exposure to stinging insects; in such cases, improving the quality of life can be sufficient justification for treatment. There are limited data on adults with strictly cutaneous systemic reactions, but there are cases of progression in adults from urticaria alone to life-threatening anaphylaxis. In addition, some patients report reactions only with multiple or sequential stings, but not from isolated single stings. Therefore, because there is no test that accurately predicts which patients will have a more severe reaction, it is recommended that adults with cutaneous systemic

reactions and positive venom skin tests undergo VIT.

Fire ant immunotherapy is based on a less complete knowledge of the natural history of fire ant allergy than is available for the other Hymenoptera. Ongoing trials suggest that fire ant whole-body extract immunotherapy is reasonably safe and effective and should be employed in cases of significant systemic reactions. Current studies of fire ant immunotherapy are focused upon achieving more reliable clinical protection with improved safety.

b. Selection of venom extracts to be used for immunotherapy is entirely based upon venom skin (or serologic) test results. Therapy should include all venoms that demonstrate positive skin tests.

c. Immunotherapy schedule can follow any of several recommended schedules (see Tables 14-4 and 14-5). The common "modified rush" regimen is more rapid than "traditional" regimens, achieving the maintenance dose after eight weekly injections rather than 4 to 6 months. With this regimen, adverse reactions are no more common than in traditional regimens of inhalant allergen therapy, and the protective immune response is greater and more rapidly achieved. Rush regimens utilizing rapidly progressive doses over a period of just 2 to 3 days have also been reported to be very safe and highly effective, but more severe reactions were reported with a 210-minute rush regimen. The dosage schedule for fire ant whole-body extract immunotherapy is less well defined in terms of rapidity of buildup but most commonly follows a regimen similar to the "traditional regimen" used for venoms. Successful use of a rush immunotherapy for fire ant protocol has been published.

Table 14-4 Representative Treatment Schedule Using Pharmalgen Single Venom Preparation[a]

Week	Day	Dose no. (Each Day, at 0.5-h Intervals)	Concentration of Venom to be Used (μg/mL)	Volume for Subcutaneous Injection (mL)	Amount of Venom Injected (μg Protein)
1	1	1	0.01	0.1	0.001
		2	0.1	0.1	0.01
		3	1.0	0.1	0.1
2	8	1	1.0	0.1	0.1
		2	1.0	0.5	0.5
		3	10	0.1	1.0
3	15	1	10	0.1	1
		2	10	0.5	5
		3	10	1.0	10
4	22	1	100	0.1	10
		2	100	0.2	20
5	29	1	100	0.2	20
		2	100	0.3	30
6	36	1	100	0.3	30
		2	100	0.3	30
7	43	1	100	0.4	40
		2	100	0.4	40
8	50	1	100	0.5	50
		2	100	0.5	50
9	57	1	100	1.0	100
Monthly[b]		1	100	1.0	100

[a] The following conditions for proceeding to next dose must be observed: (i) If a single dose results in more than a moderate local reaction (wheal >5.0 cm) within 0.5 h, an additional dose should not be given during that visit. Repeat the same dose at the next visit(s) until tolerated. (ii) If a systemic manifestation of sensitivity occurs during or following a visit, or a single dose results in an excessive local reaction (wheal >10 cm) within 0.5 h, do not administer an additional dose during the visit, and reduce the total dosage for the next visit to half the total resulting in the reaction. (iii) Delayed (24–48 h) local reactions <10 cm do not require a dose adjustment. For delayed local

reactions >10 cm, hold dose at previous level.

For the mixed vespid preparation, the total venom protein concentration and the total amount of venom protein injected will be triple the amounts shown (300 µg maintenance), with no changes in injection volumes.

[b] If a patient on maintenance therapy is stung and has any systemic manifestation of sensitivity, the maintenance dosage should be increased to 200 µg for the relevant venom, using increments no >50 µg.

(From Pharmalgen venom extract treatment schedule. Round Rock TX: ALK-Abello Laboratories, with permission.)

Table 14-5 Representative Treatment Schedule Using Venomil Single Venom Preparation[a]

Week number	Concentration of Venom to be Used (µg/mL)	Volume for Subcutaneous Injection (mL)	Amount of Venom Injected (µg Protein)
1	1	0.05	0.05
2	1	0.10	0.1
3	1	0.20	0.2
4	1	0.40	0.4
5	10	0.05	0.5
6	10	0.10	1
7	10	0.20	2
8	10	0.40	4
9	100	0.05	5
10	100	0.10	10
11	100	0.20	20
12	100	0.40	40
13	100	0.60	60
14	100	0.80	80
15	100	1.00	100
16	100	1.00	100
18	100	1.00	100
21	100	1.00	100
Monthly	100	1.00	100

[a]Precaution regarding progression is similar to that in Table 14-4.

Multiple venom sensitivities are treated with individual single venom preparations given simultaneously at separate sites. (Except, if the patient has separate sensitivities to yellow jacket, yellow hornet, and white-faced hornet venoms concurrently, the patient can receive mixed vespid venom protein.) Patients with such sensitivities have an increased risk of systemic reactions. (From Venomil hymenoptera treatment schedule. Spokane, WA: Jubilant HollisterStier LLC, with permission.)

d. Maintenance dose should be 100 µg of each of the venoms giving positive skin (or serologic) test. VIT is at least 98% effective in completely preventing systemic allergic reactions, but lower doses (<100 µg) may not provide complete protection in 15% to 20% of patients. The same dose has been recommended to children age 3 years and older, but new evidence suggests that 50 µg may be sufficient. Incomplete protection with systemic reaction to subsequent stings (albeit milder than pre-VIT sting reactions) occurs in only 2% of patients treated with multiple vespid venoms, 10% of those treated with a single vespid venom, and 20% of those treated with honeybee venom. Such patients can be fully protected with higher (150 to 250 µg) doses. For imported fire ant immunotherapy with either *Solenopsis invicta* or a mixture of *S. invicta* and *S. richteri*, 0.5 mL of a 1:200 wt/vol extract is the most widely prescribed maintenance dose. Special dosing might need to be considered for treatment failures with any insect immunotherapy.

e. Interval of maintenance injections should be every 4 weeks for at least 1 year. Most experts agree that the maintenance interval may then be increased to every 6 to 8 weeks during the next 1 to 3 years.

f. Monitoring VIT

i. Venom-specific IgG measurement is useful to determine whether VIT is producing a protective response. Venom-specific IgG can be quantitated 2 to 3 months after a maintenance dose has been reached and then after 2 to 3 years of treatment to determine whether the venom-specific IgG concentration is adequately maintained when injections are given less frequently (i.e., 6- to 8-week interval).

ii. Venom skin tests and serologic tests may be repeated every 2 to 3 years to determine if and when there has been a significant decline in venom-specific IgE. Skin tests generally remain unchanged in the first 2 to 3 years but may show a significant decline after 4 to 6 years. Less than 20% of patients become skin test negative after 5 years, but 50% to 60% become negative after 7 to 10 years.

g. Adverse reactions

VIT causes reactions no more frequently than inhalant allergen immunotherapy. Large local reactions are common, occurring in up to 50% of patients, especially in the dose range of 20 to 50 μg. Unlike standard inhalant immunotherapy, there is a uniform target dose in VIT, so it is often necessary to advance the dose in the face of moderately severe local reactions. Systemic reactions occur after immunotherapy injections in 10% to 15% of patients during the initial weeks of treatment, regardless of the regimen used. Most reactions are mild, and fewer than half require epinephrine. Premedication with antihistamine is associated with fewer local and systemic reactions to injections and fewer systemic reactions to stings (i.e., improved protection). In the unusual case of recurrent systemic reactions to injections, therapy may be streamlined to a single venom and given in divided doses, 30 minutes apart. If necessary, rush VIT using a desensitization protocol, with or without omalizumab, has been highly successful.

h. Discontinuing treatment

i. General. The product package insert, unchanged since its inception 33 years ago, states that therapy should be continued indefinitely. However, long-term follow-up studies of adults and children demonstrate that VIT can, in most cases, be stopped after 5 years, even in the presence of persistent positive skin tests. Observation of patients for 5 to 10 years after completing 5 to 8 years of venom treatment (mean 6 years) has shown a 10% chance of systemic symptoms each time he or she is stung but only a 2% risk of a reaction requiring epinephrine treatment. Additional stings over a period of years lead to a cumulative frequency of 16% for systemic reactions after stopping VIT. Patients who show a higher frequency of significant systemic reactions include those who have had a systemic reaction (to a sting or an injection) during the period of VIT and those receiving honeybee VIT. Although studies differ on whether there is a higher reaction rate in patients with a history of very severe pretreatment sting reactions than in the patients who had milder reactions, experts agree that these patients are more prone to any reaction being more severe. Patients who had life-threatening reactions should be considered for indefinite treatment. There is also a marked increase in risk of sting anaphylaxis (including death) if VIT is stopped in patients with mastocytosis.

ii. Children. Insect allergy in children is said to have a more benign and transient course than in adults. Some surveys indicate up to 50% loss of sensitivity over a 10-year period in children and young adults. In a long-term follow-up of the hundreds of children evaluated

in the Johns Hopkins program 15 to 20 years ago, the frequency of systemic reaction to subsequent stings was significantly lower (3%) in those who had received a course of VIT than those who did not (17%). Among the untreated patients, the reaction rate was higher in those with a history of moderate to severe reactions (32%) than in patients who had had milder reactions (13%). These results suggest that children with mild systemic reactions do have a benign course. Those who have more severe reactions have a high residual risk up to 15 years later, which can be eliminated (or averted) by a course of immunotherapy. VIT induces lasting tolerance more efficiently in children (98%) than in adults (84%) when evaluated more than 10 years after stopping VIT.

BITING INSECT ALLERGY

Although stinging insects cause most insect-related systemic reactions, anaphylaxis has been reported in a small number of cases from biting insects. Allergic reactions to biting insects are more commonly manifest by large local swellings. There are also inhalant allergies (rhinitis and asthma) from the airborne allergens produced by certain insects, both indoors (e.g., cockroach and ladybug) and outdoors (caddis fly and midge). Materials for testing are commercially available for some of these biting and inhalant insect allergens, but there are few studies of their diagnostic utility or predictive value.

Mosquito allergy is not uncommon and causes large local inflammatory reactions to the salivary antigens. Children with multiple such reactions are said to have "skeeter syndrome." Like other large local reactions, antihistamines help the itching, but not the swelling. Oral prednisone is effective, but the reactions can be frequent, and this could lead to significant steroid side effects. Commercial mosquito extracts are of uncertain value, and the allergens have been sequenced and synthesized, and research is proceeding to prepare a clinically useful product.

Triatoma (kissing bug) allergy may manifest as systemic reactions of variable severity. Characteristically, these insects are early morning feeders, and bites usually occur on exposed areas (e.g., arms and face) while the individual is sleeping. *Triatoma* live in warm climates, especially in the southwestern and southeastern United States, Texas, and the Gulf states. Rodents are common vectors. Allergy to these biting insects is uncommon, and anaphylactic reactions usually occur in individuals with repeated bites.

Treatment of allergic reactions to biting insects is directed to symptomatic management of the acute reaction and to avoidance precautions, as with Hymenoptera sensitivity. In the case of *Triatoma* allergy, immunotherapy using a salivary gland extract was demonstrated to be effective. However, no commercial extract is currently available.

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15
Drug Allergy

David A. Khan

Adverse drug reactions (ADRs) are defined as any noxious, unintended, and undesired effect of a drug that occurs at doses used for prevention, diagnosis, and treatment. ADRs are common in both the inpatient and outpatient setting. Prospective studies have shown that 15% of hospitalized patients had ADRs and 6.7% experienced serious reactions. In the outpatient setting, as many as 25% of patients report ADRs. While ADRs are relatively common, drug allergic reactions account for a minority of these.

ADRs are categorized into predictable (type A) and unpredictable (type B) reactions. Predictable reactions account for about 80% of ADRs and are related to the known pharmacologic effects of the drug, often dose dependent, and are not typically related to patient-specific factors. Examples of predictable ADRs include sedation from antihistamines, nephrotoxicity from aminoglycosides, and drug interactions. Unpredictable reactions are unrelated to the pharmacologic activity of the drug, occur in susceptible individuals, and are generally not dose dependent. Drug intolerances and idiosyncratic reactions (e.g., dapsone-induced hemolysis in glucose-6-phosphatase deficiency) are unpredictable ADRs. Drug allergic reactions are classified as unpredictable ADRs and are the focus of this chapter.

The term drug allergy has been used by some to describe only IgE-mediated drug reactions. However, in this chapter, the term drug allergy is used in a much broader sense to include both immune and non–immune-mediated reactions, which result in a variety of inflammatory responses.

I. IMMUNOLOGIC MECHANISMS OF DRUG ALLERGY

A. Currently, three hypotheses have been proposed to explain immunologic mechanisms of drug allergy. The **hapten hypothesis** explains how small molecules that would typically be nonimmunogenic can result in sensitization and allergy. Penicillin is the best studied and has been shown to bind to self-proteins (e.g., albumin) and to stimulate an immune-specific response to the penicillin–albumin conjugate. The hapten–protein interaction leads to presentation of a hapten-modified peptide by MHC molecules in which a complete immune response with T and B cells often occurs.

B. A similar hypothesis is the **prohapten hypothesis**. The prototypical example is sulfamethoxazole, which itself is not protein reactive but gains reactivity through liver metabolism eventually to a nitroso intermediate (N^4-sulfonamidoyl), which covalently haptenates human serum proteins.

C. The most recent hypothesis is termed the "**p-I concept**" (pharmacologic interaction with immune receptors). This hypothesis states that drugs may interact directly with immune receptors, such as T-cell receptors or MHC molecules. Carbamazepine is an example of a drug that elicits a strong T-cell response but no antibodies indicative of a p-I interaction. Some drugs may cause drug allergic reactions through more than one mechanism (e.g., sulfonamides may involve prohapten

and p-I concept mechanisms).

II. IMMUNOPATHOLOGY OF DRUG ALLERGY

A. Drug allergic reactions have a wide diversity of immunopathology. Many drug reactions can be readily classified using the **Gell and Coombs system of hypersensitivity**.

1. The most common form of drug allergic reactions (maculopapular exan-thems) are considered **Type IV delayed-type hypersensitivity (DTH) reactions**. Type IV reactions can be subdivided into four categories involving activation and recruitment of monocytes (IVa), eosinophils (IVb), CD4+ or CD8+ T cells (IVc), and neutrophils (IVd). In addition to maculopapular exanthems, Type IV drug reactions may also present with eczematous, pustular, or bullous lesions.
2. **Type I immediate reactions** to drugs are another common form of drug allergy and are mediated by drug-specific IgE antibodies. Clinical manifestations of type I reactions may include urticaria, angioedema, bronchospasm, and anaphylaxis.
3. **Type II hypersensitivity reactions** are **cytotoxic** reactions mediated by drug-specific IgG or IgM antibodies. Cytotoxic drug reactions most commonly affect cells of the hematopoetic system and may present as hemolytic anemia, thrombocytopenia, or granulocytopenia.
4. **Type III immune complex–mediated reactions** are the least common of the Gell and Coombs hypersensitivity reactions from drugs and usually present with serum sickness.

B. Several other well-characterized immunologic reactions to drugs have been described, which do not fit into the Gell and Coombs hypersensitivity paradigm.

1. **Pseudoallergic reactions** resemble type I hypersensitivity clinically but are not caused by IgE-mediated reactions. The pathogenesis of pseudoallergic reactions relates to IgE-independent mast cell activation. Opiates, vancomycin, and radiocontrast media (RCM) may all cause pseudoallergic reactions.
2. Drugs may also cause **complement activation, release of bradykinin, or other innate immune responses**.
3. **Severe cutaneous adverse reactions (SCARs)** have variable immuno-pathology and include three separate syndromes: (1) Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), (2) drug rash with eosinophilia and systemic symptoms (DRESS), and (3) acute generalized exanthematous pustulosis (AGEP).

   a. SJS and TEN are now thought to represent a spectrum of a single type of reaction. The basic epidermal pathology in TEN is large-scale epidermal death, the result of apoptosis. The exact mechanism of apoptosis in TEN is unknown but may involve granzymes, granulysin, tumor necrosis factor (TNF), and Fas ligand as effectors of apoptosis.

   b. The pathogenesis of **DRESS** is not completely understood. Failure of drug detoxification pathways leading to an accumulation of harmful metabolites has been hypothesized to explain DRESS from anticonvulsants. Drug-specific T cells and reactivation of human herpesvirus 6 may also be involved with the pathogenesis of DRESS.

   c. AGEP is primarily thought to represent a type IVc delayed hypersensitivity

response with drug-specific T cells, causing a predominantly neutrophilic dermal reaction.

4. **Noncutaneous organ–specific immunologic drug reactions** include immunologic hepatitis, nephropathies (interstitial nephritis, membranous glomerulonephritis), and pulmonary hypersensitivity (pneumo-nitis, edema, granulomatosis, and fibrosis). Drug-induced vasculitis, drug-induced granulomatous disease, and drug-induced lupus may be organ specific or have multiorgan involvement.

III. RISK FACTORS

Several factors are likely involved in the development of drug allergy including chemical properties of the drug, amount, route and duration of exposure, and several host factors.

A. Several **properties related to the drug** itself may be risk factors. Large-molecular-weight agents (e.g., proteins) and some polysaccharides are immunogenic themselves, while most smaller drugs act as haptens to induce allergic responses. Oral administration appears less likely to elicit allergic reactions compared to parenteral or cutaneous administration. Higher doses and more frequent, repetitive administration are associated with greater sensitization.

B. Host risk factors for drug allergies include female gender and concurrent medical illnesses. Children and the elderly have a lower incidence of drug allergic reactions. Atopy is associated with some drug allergic reactions, including both IgE-mediated and non–IgE-mediated reactions (e.g., pseudoallergic reactions to radiocontrast dye). Patients with mastocytosis are at risk for reactions to nonspecific mast cell–activating drugs such as narcotics and vancomycin.

IV. PHARMACOGENETICS AND DRUG ALLERGY

Associations between HLA haplotypes and specific drug reactions have been recognized for several years. However, recently, several specific HLA alleles have been associated with specific drug reactions, and screening for certain alleles has been recommended prior to drug therapy. The best example is the association of HLA-B*5701 and the development of the abacavir hypersensitivity syndrome. Abacavir is a nucleoside reverse transcriptase inhibitor that has been associated with a multiorgan hypersensitivity reaction in approximately 4% of patients. Symptoms and signs of abacavir hypersensitivity include fever, rash, malaise, and gastrointestinal and respiratory symptoms. A very strong association of HLA-B*5701 was discovered, and screening for this allele has been shown to reduce abacavir hypersensitivity reactions (confirmed by patch testing). Table 15-1 outlines specific drugs and alleles associated with severe drug reactions. It is important to note that pharmacogenetics are dependent on the specific drug and, in some cases (e.g., carbamazepine), the ethnicity of the patient.

Table 15-1 Pharmacogenetic Associations in Drug Allergy

Drug	Allele	Ethnic Associations	Drug Reaction	Genetic Screening Recommended
Carbamazepine	HLA-B*1502	Han Chinese	Stevens–Johnson syndrome	Yes
Allopurinol	HLA-B*5801	Han Chinese, European, Japanese	SCAR	No
Abacavir	HLA-B*5701	Multiple ethnicities (not Japanese)	Abacavir hypersensitivity syndrome	Yes

SCAR, severe cutaneous adverse reaction.

V. DRUG ALLERGIC SYNDROMES

Drug allergic reactions can present with a variety of presentations, as shown in Table 15-2. Most reactions are organ specific, but some can involve multiple organs.

Table 15-2 Manifestations of Drug Allergic Reactions

	Organ-Specific Reactions	
	Clinical Features	Examples of Causative Agents
Cutaneous		
• Exanthems	Diffuse fine macules and papules evolve over days after drug initiation; often delayed-type hypersensitivity	Allopurinol, aminopenicillins, cephalosporins, antiepileptic agents, and antibacterial sulfonamides
• Urticaria angioedema	Onset within minutes of drug initiation, potential for anaphylaxis, often IgE-mediated	IgE-mediated: beta-lactam antibiotics Bradykinin mediated: ACE-I
• Fixed drug eruption	Hyperpigmented plaques recur at same skin or mucosal site	Tetracycline, NSAIDs, and carbamazepine
• Pustules	Acneiform, AGEP	Acneiform: corticosteroids, sirolimus AGEP: antibiotics, calcium channel blockers
• Photodistributed	Eczematous (photoallergic, cutaneous lupus) erythroderma (phototoxic)	Photoallergic: quinidine, Hydrochlorothiazide Phototoxic: sulfonamides, tetracycline, furosemide, fluoroquinolones
• Lichenoid	Violaceous, polygonal papules	ACE-I, furosemide, NSAIDs, proton pump inhibitors, imatinib
• Bullous	Tense blisters Flaccid blisters	Furosemide, vancomycin Captopril, penicillamine
• Cutaneous lupus	Erythematous/scaly plaques in photodistribution	Hydrochlorothiazide, calcium channel blockers, ACE inhibitors
Hematologic	Hemolytic anemia, thrombocytopenia, granulocytopenia	Penicillin, quinine, sulfonamides
Hepatic	Hepatitis, cholestatic jaundice	Para-aminosalacylic acid, sulfonamides, phenothiazines
Pulmonary	Pneumonitis, fibrosis	Nitrofurantoin, bleomycin, methotrexate
Renal	Interstital nephritis, membranous glomerulonephritis	Penicillin, sulfonamides, gold, penicillamine, allopurinol

Multiorgan Reactions

	Clinical Features	Examples of Causative Agents
Anaphylaxis	Urticaria/angioedema, bronchospasm, gastrointestinal symptoms, hypotension IgE- and non–IgE-dependent reactions	Beta-lactam antibiotics, monoclonal antibodies
SCAR (Severe cutaneous adverse reactions)		
• Drug rash with eosinophilia and systemic symptoms	Cutaneous, fever, eosinophilia, hepatic dysfunction, lymphadenopathy	Anticonvulsants, sulfonamides, minocycline, allopurinol
• Stevens-Johnson syndrome	Fever, erosive stomatitis, ocular involvement, purpuric macules on face and trunk with <10% epidermal detachment	Antibacterial sulfonamides, anticonvulsants, oxicam NSAIDs, nevirapine, lamotrigine, sertraline, pantoprazole, tramadol
• Toxic epidermal necrolysis	Similar features as SJS but >30% epidermal detachment mortality as high as 50%	Same as SJS
Serum sickness	Urticaria, arthralgias, fever	Heterologous antibodies, infliximab
Systemic lupus erythematosus	Arthralgias, myalgias, fever, malaise	Hydralazine, procainamide, isoniazid
Vasculitis	Cutaneous or visceral vasculitis	Hydralazine, penicillamine, propylthiouracil

(Modified from Khan DA, Solensky R. Drug allergy. *J Allergy Clin Immunol* 2010;125(2 Suppl 2):S126–S137.)

A. Cutaneous reactions

1. Exanthems

The most common cutaneous manifestation of drug allergic reactions is a generalized exanthem (a.k.a. maculopapular eruption). These lesions are pruritic, often beginning as macules that can evolve into papules and eventually may coalesce into plaques. Drug-induced exanthems are pru-ritic and typically involve the trunk and spread outward to the limbs in a bilateral symmetric pattern. Many drug-induced exanthems are considered delayed-type hypersensitivity reactions and typically evolve after several days of being on the offending drug. With resolution of an exanthem, scaling may occur. This should be distinguished from the type of epidermal detachment seen in severe cutaneous reactions that occurs early in the reaction. Drug-induced exanthems do not evolve into anaphylactic reactions as they are not IgE-mediated reactions. Numerous drugs are capable of causing exanthems.

2. Urticaria and angioedema

Urticaria and angioedema are the most common manifestations of IgE-mediated drug allergy. It is important to recognize that non–IgE-mediated drug allergic reactions can also manifest with urticaria and angioedema. Urticaria is the most common manifestation of serum sickness; however, the presence of maculopapular lesions of the sides of the fingers and toes or a serpiginous distribution of such lesions along lateral aspects of both soles may be more specific for serum sickness. Angioedema due to ACE inhibitors is likely a bradykinin-mediated manifestation of angioedema. Complement activation may also present with urticaria and angioedema. Urticarial lesions are raised, erythema-tous, pruritic lesions that wax and wane and range in size from a few millimeters to several inches in diameter. Angioedema presents as swelling of the tissues and may not be pruritic

or erythematous. It has a predilection for the lips and eyelids but may occur almost anywhere.

3. **Fixed drug eruptions**
   Fixed drug eruptions recur at the same skin or mucosal site upon reintroduction of the causative drug. Fixed drug eruptions typically develop within 1 to 2 weeks of drug exposure but may recur more rapidly with subsequent reexposure. Fixed drug eruptions are pleomorphic and may present as eczematous lesions, papules, vesicles, or urticaria. Lesions are often round or oval, sharply demarcated, red to livid, slightly elevated plaques, ranging from a few millimeters to several centimeters in diameter. They may also present with mucosal lesions that are usually bullous. Fixed drug eruptions have a predilection for the lips, hands, and genitalia (especially in men). Fixed drug eruptions can occur with a number of medications including tetracycline, nonsteroidal anti- inflammatory drugs, and carbamazepine.
4. **Eczematous reactions**
   Drug reactions may present as eczematous lesions. Biologics such as infliximab may cause eczematous lesions with a similar distribution as atopic dermatitis. **Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE)** specifically refers to a symmetric drug eruption after systemic exposure with distinctive sharply demarcated erythema of the buttocks and/or V-shaped erythema of the thighs along with involvement of at least one other flexural area and the absence of systemic symptoms. SDRIFE was previously referred to as baboon syndrome. While it most commonly presents as an exanthema, SDRIFE lesions may also be papules, pustules, or vesicles.
5. **Exfoliative dermatitis**
   Exfoliative dermatitis is characterized by widespread erythroderma and marked scaling involving >90% of the skin surface. Many more benign cutaneous eruptions can progress to exfoliative dermatitis. Several systemic manifestations can occur including hypothermia, edema, anemia, leukocytosis, and hypoalbuminemia.
6. **Photodistributed drug reactions**
   Photoallergic reactions are DTH reactions and may present with eczematous eruptions in a photodistribution on the face, "V" area of the neck, dorsa of hands, and arms, with sparing of scalp and submental and periorbital areas. Photoallergic reactions typically develop within days of drug and ultraviolet light exposure. **Phototoxic** reactions typically present with erythroderma within minutes to hours of sunlight exposure but may present with vesicles with severe reactions. Drug-induced cutaneous lupus may also present with eruptions in a photodistribution, typically with erythema, or scaly, annular plaques.
7. **Lichenoid eruptions**
   Some drug reactions may manifest as lichenoid reactions with violaceous, polygonal papules. Eruptions may resemble lichen planus. Medications associated with lichenoid eruptions include ACE-I, furosemide, gold, NSAIDs, proton pump inhibitors, and imatinib.
8. **Pustular drug eruptions**
   Several cutaneous drug reactions may present with pustules. Acne can occur with glucocorticoids, androgens, lithium, phenytoin, and iso-niazid and is quite common with the

immunosuppressant sirolimus. **AGEP** is a rare type of drug eruption that begins with erythema or edema in the intertriginous areas or face. Afterward, fine nonfollicular sterile pustules develop. Fever, neutrophilia, and, in one-third of cases, eosinophilia may also be present. Atypical target lesions, blisters, and oral mucosal involvement are uncommon but may be confused with SJS. Implicated drugs include antibiotics, with development of lesions within a few days. In contrast, AGEP from calcium channel blockers typically develops after a period of weeks after drug initiation. Finally, **drug-induced Sweet's syndrome** may present with fever, painful nodules, pustules, plaques, and a neutrophilic dermatosis. The onset of drug-induced Sweet's syndrome is variable over weeks to months after drug initiation. Granulocyte colony-stimulating factor (G-CSF), sulfonamide antibiotics, and minocycline may all cause a drug-induced Sweet's syndrome.

9. Vesicular/bullous drug eruptions

Drug allergic reactions may also present with vesicles or bullae. Some of these reactions are relatively benign and self-limited, while others are classified as SCAR. **Drug-induced pemphigus** presents with flaccid blisters and is most often caused by drugs containing a thiol group (e.g., captopril, penicillamine). **Drug-induced bullous pemphigoid** presents with tense bullae on extremities, the trunk, and occasionally mucous membranes. ACE inhibitors, furosemide, penicillin, and sulfasalazine are some of the causative drugs implicated in drug-induced bullous pemphigoid. **Linear IgA bullous disease** causes a clinically similar eruption, and vancomycin is the most commonly incriminated drug. Vancomycin-induced linear IgA bullous disease is not dose dependent, and the severity does not appear to correlate with serum vancomycin levels. **Erythema multiforme major (EMM)** have target lesions with or without blisters. Clinically, EMM is similar to SJS, but there are important differences. The distribution of lesions is symmetric, mainly acral distribution in EMM, and mucosal involvement is less severe and extensive and involves two or more mucosal lesions less frequently then SJS. EMM occurs mainly after herpes simplex infection and less frequently is drug induced, and the prognosis is usually benign. In addition to SJS, TEN and DRESS may also present with vesicular or bullous lesions.

10. Purpuric/petechial drug reactions

The presence of purpura and petechiae are often cutaneous stigmata of **vasculitis,** which can be drug induced. A number of different types of drug-induced vasculitic reactions have been reported. A wide variety of drugs have been implicated, and the onset of cutaneous symptoms may occur after years of therapy with the offending drug.

11. Severe cutaneous adverse reactions

SCARs are composed of three distinct types of cutaneous reactions with systemic manifestations and include AGEP, SJS/TEN, and DRESS.

a. AGEP

Acute generalized eczematous pustulosis (AGEP) is a rare type of drug eruption that begins with erythema or edema in the inter-triginous areas or face. Afterward, fine nonfollicular sterile pustules develop. Fever, neutrophilia, and, in one-third of cases, eosinophilia may also be present. Atypical target lesions, blisters, and oral muco-sal involvement are uncommon but may be confused with SJS. Implicated drugs include antibiotics and calcium channel blockers. AGEP is T cell–mediated drug reaction, with

drug-specific CXCL8 T cells secreting IL-8 resulting in a neutrophilic dermatitis. While classified as a SCAR, AGEP has a good prognosis with symptoms resolving within days of drug discontinuation with rare complications, more often in the elderly.

b. SJS/TEN

SJS and TEN are considered part of a single disease spectrum. A common classification separates these conditions based on the degree of body involvement. **SJS** is classified as having <10% total body surface area; between 10% and 30% body surface area is considered **overlap SJS/TEN;** and involvement of >30% is classified as **TEN.** The majority of SJS is drug induced, and TEN is almost always drug induced. Clinical features of SJS/TEN include a triad of mucous membrane erosions, target lesions, and epidermal necrosis with detachment. A prodromal phase of fever, cough, and malaise may precede cutaneous findings by a few weeks. Target lesions, which may evolve from three-ringed iris lesions to purpuric two-ringed lesions, often first appear on the trunk, then rapidly spread to the face, neck, and extremities, usually peaking in 4 days. Blisters of SJS/TEN are flaccid, and there may be a positive **Nikolsky's sign** (slight rubbing of skin results in epidermal detachment), especially in TEN. Mucosal lesions develop with painful lesions involving the lip, oral cavity, conjunctiva, nasal cavity, urethra, and vagina. Corneal involvement may result in ulceration, perforation, and sclerotic corneal changes. Multiorgan involvement including the gastrointestinal tract and hepatic, pulmonary, and renal involvement may also occur with SJS/TEN. Over a hundred drugs have been implicated as causes of SJS/TEN. Drugs associated with a high relative risk of developing SJS/TEN include sulfonamide antibiotics, cephalosporins, carbamazepine, phenytoin, and oxicam NSAIDs. More recent surveys have indicated that nevirapine, lamotrigine, sertraline, pantoprazole, and tramadol have also been associated with a higher risk of SJS/TEN. Prognostic factors and a TEN scoring system have been developed for TEN and include risk factors of age, malignancy, tachycardia, epidermal detachment at admission, renal function, hyperglycemia, and acidosis.

c. DRESS

The **drug rash with eosinophilia and systemic symptoms** syndrome is a drug-induced, multiorgan inflammatory response that may be life threatening. The terminology describing this syndrome has varied in the literature, with various terms preferred by some authors, and includes terms such as phenytoin hypersensitivity syndrome, drug hypersensitivity syndrome, drug-induced hypersensitivity syndrome, and drug-induced delayed multiorgan hypersensitivity syndrome. Characteristic features of DRESS vary and may include various cutaneous eruptions, fever, eosinophilia (most but not all cases), hepatic dysfunction, renal dysfunction, and lymphadenopathy. Cutaneous manifestations typically include maculopapular exanthems, but vesicles, bullae, pustules, target lesions, and erythroderma may also be seen. Facial edema, which is often diffuse, occurs frequently in DRESS and can be mistaken for angioedema. Extremity and genital edema can also occur. Hypotension has been reported in up to 42% of DRESS patients. Multiorgan involvement including liver, kidney, lungs, heart, joints, and brain can often occur, and some cases of hypogammaglobulinemia have been reported in association with DRESS. Proposed inclusion criteria for DRESS include

three or more of the following: hospitalization, reaction suspected to be drug-related, acute skin rash, fever >38°C, enlarged lymph nodes in at least two sites, involvement of at least one internal organ, and hematologic abindentities. Medications implicated in DRESS include anticonvul-sants, sulfonamides, allopurinol, minocycline, dapsone, sulfasalazine, abacavir, nevirapine, vancomycin, and NSAIDs. DRESS is atypical from other drug allergic reactions in that the reaction develops later, usually 2 to 8 weeks after therapy is started; symptoms may worsen after the drug is discontinued; and symptoms may persist for weeks or even months after the drug has been discontinued. Human herpes-virus 6 reactivation has been detected in many patients with DRESS within 2 to 3 weeks of the eruption and may be an indicator of more severe disease.

B. Drug-induced vasculitis

Vasculitis from drugs may present with cutaneous signs or have systemic involvement. Numerous drugs from a variety of therapeutic areas have been implicated in drug-induced vasculitis including propylthiouracil, hydrala-zine, G-CSF, cefaclor, minocycline, allopurinol, D-penicillamine, phenytoin, isotretinoin, and methotrexate. Some drugs are associated with antineutrophil cytoplasmic antibodies including propylthiouracil, hydralazine, allopu-rinol, minocycline, penicillamine, and phenytoin. These medications can induce severe systemic vasculitic syndromes resembling microscopic poly-angiitis, Wegener's granulomatosis, and polyarteritis nodosa. As mentioned previously, there can be a very long latency (e.g., years) prior to development of vasculits from certain drugs. Churg-Strauss syndrome has also been reported to occur in association with certain asthma medications including leukotriene modifiers, inhaled corticosteroids, and omalizumab. Several theories have been postulated including that the drug causes a steroid-sparing effect with an "unmasking" of the already present but unidentified vasculitis. To date, a cause and effect relationship for asthma medications and Churg-Strauss syndrome remains to be established.

C. Drug-induced lupus

Drug-induced lupus erythematosus (DILE) is thought to represent up to 10% of systemic lupus erythematosus cases. Similar to idiopathic lupus, DILE can have systemic forms as well as predominantly cutaneous forms.

1. **Systemic DILE** usually occurs after years of exposure to the offending drug and resolves within weeks to months after withdrawal of the causative agent. The most frequent signs and symptoms of systemic DILE are arthralgias, myalgias, fever, malaise, and weight loss. Procainamide and hydralazine are the most frequently implicated drugs, but causal evidence is also convincing for isoniazid, methyldopa, quinidine, mino-cycline, and chlorpromazine. Hypocomplementemia and antibodies to double-stranded DNA (dsDNA) are rare, while antihistone antibodies are present in >90% of patients with DILE overall but occur less frequently with minocycline, propylthiouracil, and statins. DILE related to anti-TNFα drugs demonstrates several differences from classic DILE including more frequent rash, antibodies to dsDNA (90%), hypocom-plementemia, and less frequent antihistone antibodies.
2. **Cutaneous DILE** differs from systemic DILE in several aspects. Drugs most commonly associated with cutaneous DILE include hydrochlorothi-azide, calcium channel blockers, ACE inhibitors, and systemic antifungal agents. Anti-Ro and anti-SSA antibodies are

usually present in cutaneous DILE, while antihistone antibodies are much less frequent. The onset of cutaneous DILE is much faster than systemic DILE, with disease being triggered typically in 4 to 8 weeks.

D. Serum sickness

Serum sickness is a clinical syndrome mediated by immune complex hypersensitivity. It is characterized by fever, lymphadenopathy, arthralgias, cutaneous eruptions, gastrointestinal disturbances, and may be associated with proteinuria. Symptoms typically appear 1 to 3 weeks after starting an offending drug but may occur more rapidly in previously sensitized individuals. Serum sickness was first described with heterologous antisera such as snake antivenom. Subsequently, many small-molecular-weight drugs have been found to be associated with serum sickness–like symptoms. These include penicillin, sulfonamides, thiouracils, and phenytoin. Monoclonal antibody therapies have also been associated with serum sickness–like reactions to several agents including infliximab, rituximab, omalizumab, and natalizumab. The prognosis for complete recovery is excellent; however, symptoms may last as long as several weeks. Treatment consists of systemic corticosteroids and H1 antihistamines and, in some cases, NSAIDs.

Serum sickness–like reactions have also been described with symptoms of erythema multiforme and arthralgias with or without fever, but no evidence for immune complexes, hypocomplementemia, vasculitis, or renal disease. In children, cefaclor is the most common drug associated with serum sickness–like reactions. Serum sickness–like reactions to cefaclor are thought to result from altered metabolism of the parent drug resulting in toxic reactive intermediate compounds. *In vitro* tests for toxic metabolites have shown a lack of cross-reactivity between cefaclor and loracarbef, but confirmation of lack of clinical cross-reactivity has not been well studied.

E. Immunologic nephropathy

The most common type of an immunologic drug-induced nephropathy is acute interstitial nephritis. Antimicrobials and NSAIDs are the most common cause, and reactions may include extrarenal manifestations such as fever, rash, arthalgias, and peripheral eosinophilia. Eosinophiluria lacks both specificity and sensitivity for a diagnosis of acute interstitial nephritis. Other types of immunologic drug-induced conditions include membranous glomerulone-phritis (e.g., with gold, penicillamine, and allopurinol) or renal vasculitis.

F. Immunologic hepatitis

Many drugs have been implicated with a hypersensitivity-causing hepatitis including NSAIDs, sulfonamides, antidepressants, and halothane. Allergic hepatitis may also be seen in DRESS. Clinically, both hepatocellular injury and cholestasis can occur, and most episodes have a good prognosis with discontinuation of the drug. Resolution of the hepatitis may take 1 to 3 months upon discontinuation but, in some cases, may be associated with fulminant hepatitis, which is associated with high mortality.

G. Pulmonary drug hypersensitivity

Drug-induced pulmonary hypersensitivity can have several manifestations including interstitial lung disease (ILD), alveolar damage (e.g., edema, hemorrhage, pneumonitis), and vasculitis. Numerous drugs can cause the syndrome of pulmonary infiltrate with eosinophilia,

but antibiotics and NSAIDs are among the most common. Other classes of drugs implicated in this syndrome include anticonvulsants, antidepressants, and cardiovascular medications including ACE-I, beta blockers, and amiodarone.

Certain drug-induced pulmonary reactions are worth mentioning specifically.

1. **Amiodarone** has been associated with various pulmonary reactions including interstitial pneumonitis, bronchiolitis obliterans, and acute respiratory distress syndrome, with some reactions thought to be immu-nologic in origin.
2. **Methotrexate** is well known to be associated with an acute granuloma-tous ILD.
3. A number of **chemotherapeutics** have been associated with ILD that may progress to fibrosis including bleomycin, mitomycin-C, busulfan, cyclophosphamide, and nitrosourea drugs.
4. **Nitrofurantoin** is the most commonly reported antimicrobial causing pulmonary toxicity. The acute form of nitrofurantoin pulmonary toxicity is a hypersensitivity reaction and may develop hours to days after treatment. Symptoms may include fever, dyspnea, cough, and rash, with radiographic findings showing a diffuse reticular pattern with basilar predominance. Peripheral eosinophilia is common in acute nitrofurantoin pulmonary reactions.

VI. EVALUATION AND DIAGNOSIS OF DRUG ALLERGY

A. History

A detailed history is the most important diagnostic tool for drug allergy. The history is critical in determining the classification of ADR, choice of diagnostic tests, safety of reintroduction of medications, and need for induction of drug tolerance procedures. When available, medical records documenting drug allergic reactions should be reviewed as patient recall is often limited and may be inaccurate.

A thorough drug allergy history can be divided into a stepwise fashion (Table 15-3).

Table 15-3 Steps in Drug Allergy History

1 Confirm history is a drug allergic reaction.
2 Classify drug allergic reaction.
3 Determine likelihood of drug(s) in question to cause reaction.
4 Determine elements that may influence drug allergy history.
5 Evaluate if subsequent exposure to drug.
6 What is likely future need of drug?

1. First, **confirm** that the "drug allergy" is indeed an allergic response. Are the symptoms and physical findings compatible with an unpredictable (type B) drug reaction?

   Was this truly a drug allergic reaction or a more predictable adverse reaction? Many patients (and some physicians) report other adverse reactions as drug allergy. For example, a history of diarrhea after taking an antibiotic is not consistent with a drug allergic reaction.

2. Attempt to **classify** the type of drug allergic reaction. For cutaneous reactions, it is important to attempt to categorize the "rash." Was it urticaria, maculopapular, bullous, etc.? Can it be classified according to the Gell and Coombs hypersensitivity, an organ-based reaction, or a well-defined drug allergic syndrome (e.g., TEN)? Is the history

compatible with an immunologic reaction? Determine the temporal relationship of exposure to the drug and the allergic reaction. Was it an immediate or more delayed reaction? Did it occur with the first dose or after therapy was completed? Was the patient previously exposed or was there an adequate time to have a period of sensitization?

3. **Determine the propensity of the drug(s) to cause the specific type of reaction** in question or other confounding factors. Has the class and chemical structure of the drug been associated with similar reactions, and if so, how often? Ensure there is no other cause for the clinical symptomatology. For example, in a patient with a drug allergy history of urticaria, is there a background of chronic urticaria?
4. Determine **other clinical elements** that may influence the drug allergy history. How long ago was the drug exposure? Certain drug allergic responses (e.g., penicillin) wane over time. What was the clinical indication for administration of the drug? For example, a child who received an antibiotic in the setting of an upper respiratory infection and develops a delayed pruritic eruption is more often due to concomitant viral illness rather than the antibiotic. How severe was the reaction (e.g., hos-pitalization required)? What was the duration of symptoms (minutes vs. hours vs. days)? Was any treatment required? Does the patient have any associated conditions that may increase propensity of drug reactions or be a confounder for drug reactions (e.g., HIV, chronic skin disease)? Were other medications involved? NSAIDs and opiates can be missed as true causes of drug reactions.
5. Determine if there has been **subsequent exposure** to the drug or **recurrence of similar symptoms** attributed to drug. Some patients may unknowingly take a similar medication, not recognizing the name of the drug (e.g., tolerating Augmentin in a penicillin-allergic patient).
6. Finally, it is important to **determine if there is a future need** for the drug. Not all histories of drug allergies need to be evaluated. What is the likelihood a patient will need the drug again? Are suitable alternatives available? When in doubt, subspecialty consultation may be required to confirm need for a given medication.

B. Physical examination

Since drug reactions may involve virtually any organ system, a careful physical examination is recommended. Cutaneous manifestations are the most common presentation for drug allergic reactions. Characterization of cutaneous lesions is very important in regard to determining the etiology, further diagnostic tests, and management decisions. Numerous cutaneous reaction patterns have been reported in drug allergy including exanthems, urticaria, angioedema, acne, bullous eruptions, fixed drug eruptions, erythema multiforme, lupus erythematosus, photosensitivity, psoriasis, pur-pura, vasculitis, pruritus, as well as life-threatening cutaneous reactions such as SJS/TEN and DRESS. The clinical manifestations of these cutaneous reactions have been discussed earlier. Drug allergic reactions can also affect other organ symptoms, and a complete physical examination is typically appropriate. Drug reactions may present as an isolated fever, occasionally in excess of 104°F. Additionally, drug reactions may cause a wide array of physical abindentities including mucous membrane lesions, lymphade-nopathy, hepatosplenomegaly, pleuropneumonopathic abindentities, and joint tenderness/swelling.

C. Laboratory testing in drug allergy

1. **Routine laboratory evaluation** appropriate to the clinical setting may be useful for the evaluation of a patient with suspected drug reaction depending upon the history and physical exam findings. A complete blood count with a differential cell count and a total platelet count may help to exclude the possibility of cytotoxic reactions. While eosinophilia is often suggestive of a drug allergic reaction, most patients with drug allergic reactions do not have eosinophilia, and therefore, the absence of eosinophilia clearly does not exclude a drug allergic etiology. Autoantibodies may be helpful in the evaluation of drug-induced vasculitis (e.g., antinuclear cytoplasmic antibody) and DILE. In the case of systemic DILE, antihistone antibodies are frequently positive, whereas in cutaneous DILE, anti-Ro/SSA and/or anti-La/SSB are frequently positive. Immune complex assays lack sensitivity for serum sickness, and similarly hypocomplementemia may not be present either. In cases of suspect anaphylaxis, a diagnosis of anaphylaxis may be made by detecting a rise in serum total tryptase levels above baseline or in serum mature tryptase (a.k.a. β-tryptase), which peak 0.5 to 2 hours after drug administration and then decline with a $t_{1/2}$ of about 2 hours. Occasionally, biopsies of involved organs may define specific histopathologic lesions. **Skin biopsies** may be of value in the diagnosis and management of drug allergic reactions but are typically not helpful for implicating a particular drug. In complex cases where multiple drugs are involved without a clear-cut temporal relationship, a skin biopsy may be useful in suggesting a drug-induced eruption. Skin biopsies are useful in differentiating vasculitis, bullous diseases, and contact dermatitis. However, there are no absolute histologic criteria for the diagnosis of drug-induced eruptions, and a skin biopsy may not definitively exclude alternative etiologies. Furthermore, features suggestive of drug exanthems such as interface dermatitis with vacuolar alteration of keratinocytes, foci of spongiosis, and tissue eosinophilia are not specific and may be seen with other cutaneous diseases. A liver biopsy helps to differentiate between cholestatic and hepatocellular drug reactions but does not identify the specific cause. Membranous glomerulonephritis initiated by deposition of immune complexes in the kidney can be readily identified by immu-nofluorescent stains for IgG, IgM, and complement in renal biopsy specimens. Lung biopsies also may be helpful for identifying conditions such as ILD and pulmonary eosinophilia.

2. **Drug-specific testing in drug allergy**

While the history and physical examination are very useful tools in the assessment of drug-allergic patients, by themselves they are often not adequate to confirm or negate a true drug allergy. Modalities for testing for specific drug allergic reactions include skin tests, *in vitro* tests, and drug challenge. Drug challenge is the gold standard for confirming a drug allergic reaction, while skin tests and *in vitro* tests may indicate sensitization but have the potential for false-positive and false-negative results.

a. Immediate epicutaneous (prick) and intradermal skin testing

Drug skin testing using epicutaneous (prick) and intradermal methods may be used for immediate type I immunologic drug reactions. In the case of IgE-mediated drug reactions, demonstration of the presence of drug-specific IgE is usually taken as sufficient evidence that the individual is at significant risk of having a type I reaction if the drug is administered. This is helpful in the case of high-molecular-weight agents.

Penicillin is the only low-molecular-weight agent for which validated testing has been documented. Skin testing to most drugs is limited by knowledge regarding degradation products and/or metabolites and how they are conjugated with body proteins. Skin testing to native formulations of the drug may therefore lack the important immunogenic epitopes and lead to inadequate negative predictive value. Furthermore, skin testing to drugs may cause irritant reactions, and it is important to be aware of the nonirritating concentrations for drug testing (see Appendix VI). In the case of type I drug allergic reactions, skin testing to penicillin, cephalosporins, platinum-based chemotherapeutics, certain perioperative agents, and insulin may offer the best diagnostic utility and will be discussed in more detail in the sections corresponding to specific drugs.

b. Delayed skin testing

Skin testing using both intradermal and patch tests has been utilized for certain delayed immunologic drug reactions. The negative predictive values for these techniques have not been well established, and therefore, a negative test does not preclude a drug allergy.

i. The technique for performing **delayed intradermal skin tests** is similar to intradermal testing for immediate reactions, with intra-dermal injection of 0.03 to 0.05 mL to raise a 3- to 5-mm wheal. However, tests are read after 24 hours or later and considered positive when there is an infiltrated erythematous reaction. Delayed intradermal tests may be useful for drug-induced maculopapular rashes and eczema but are generally not recommended for many other cutaneous reactions and SCAR and could potentially be dangerous as cases of reactivation of DRESS have been reported after intradermal testing. Drugs that have been reported to be positive in delayed cutaneous reactions include predominantly beta-lactams, heparins, and RCM; however, other drugs have also been reported to be positive with this methodology. When directly compared, intradermal drug tests appear to be more sensitive than patch tests in most circumstances.

ii. **Patch testing** has also been utilized in delayed immunologic drug reactions in a similar fashion as intradermal tests. Nonirritating concentrations have not been firmly established for drug patch tests. Typically, drug patch testing is performed starting with 1% concentration in petrolatum, going up to a 10% concentration. A 30% concentration may be used for a pulverized tablet. Drug patch testing may be useful in fixed drug eruptions (at the residual site) and AGEP (in contrast to intradermal tests) in addition to maculopapular eruptions and other eczematous drug reactions.

c. *In vitro* tests

Several different *in vitro* tests have been utilized in drug allergy including tests for specific IgE, lymphocyte transformation tests, basophil activation tests, and a number of investigational tests that are not commercially available. Most *in vitro* tests have been evaluated in IgE-mediated reactions and, when compared to skin tests, are not as sensitive. Overall, commercially available *in vitro* tests for drug allergy require further study to determine if they are clinically useful.

i. In certain cases where skin testing is not possible (i.e., a negative histamine control test, dermatographism, or generalized eczema), **specific IgE *in vitro* assays** (e.g.,

RAST, ImmunoCAP, Immunolite) are available, though most are not adequately standardized. Immunoassays for other drugs have been even less well studied and generally lack adequate controls to validate the testing.

ii. The **lymphocyte transformation test** has been studied as an *in vitro* correlate of drug-induced cellular reactions. This test is used primarily in research studies as a retrospective test and is not clinically available in most medical centers. There is considerable disagreement among investigators about the value of this assay in evaluating drug allergies because neither its positive nor negative predictive values have been systematically investigated. The lymphocyte transformation test has recently become commercially available for selected drugs, but there are no published studies using these assays, either alone or in comparison with previous independent assays. Further data are required to determine if there is any clinical utility for commercially available lymphocyte transformation tests.

iii. The **basophil activation test** is a recently described method of evaluating expression of CD63 or CD203c on basophils after stimulation with an allergen. There are very limited data using this method to evaluate patients with possible allergies to beta-lactam antibiotics and NSAIDs. Further confirmatory studies, especially with commercially available tests, are needed before it can be accepted as a diagnostic tool.

D. Drug challenge

Graded dose challenge, drug provocation, and test dosing are all terms used to describe a procedure to determine if a patient will have an adverse reaction to a particular drug by administering lower than therapeutic doses over a period of time with observation for reactions. If a patient has a negative drug challenge, they can be considered not allergic to that drug. The rationale for starting with a lower dose is based on the concept that a smaller dose of allergen will result in a less severe and more easily treated reaction. Unlike induction of drug tolerance procedures, a graded challenge does not modify an individual's immunologic or nonimmunologic response to a given drug. Valid diagnostic tests are not available for most drugs, and therefore, it is not possible to be certain that a patient is not allergic to a drug. Importantly, drug challenges are intended for patients who, following a full evaluation, are deemed to be at low risk for being allergic to the given drug. Furthermore, the benefit of treatment with the drug should outweigh the risk of performing the drug challenge. Common indications for drug challenges include (1) excluding a drug allergy in patients with unconvincing histories of drug allergy, (2) exclude cross-reactivity of structurally related drugs, and (3) to reassure patients with histories of multiple adverse reactions to drugs. Drug challenges can be used for both immediate and delayed drug reactions. Drug challenges are usually contraindicated in several types of drug reactions such as autoimmune diseases (e.g., drug-induced lupus), SCAR, vasculitis, organ-specific drug reactions causing cytopenias, hepatitis, nephritis or pneumonitis, and serum sickness. The starting dose for graded challenge is generally higher than for induction of drug tolerance procedures, and the number of steps in the procedure may be two or several. The time intervals between doses are dependent on the type of previous reaction, and the

entire procedure may take hours or days to complete. Protocols for graded challenges for both immediate and delayed reactions are shown in Tables 15-4 and 15-5, respectively. Following a successful graded challenge and therapeutic course of the drug, future courses of the drug may be started without another challenge.

Table 15-4 Graded Challenge Protocol for History of Immediate Reactions

Likelihood of Drug Allergy	Example Scenario	No. of Steps	Starting Dose	Dose Interval and Observation[a]
Unlikely	Remote history of rash to cephalosporin	3	1/100th final dose	30 minutes between first two doses, with 1 h observation after last dose
Very unlikely	History of penicillin allergy in need of carbapenem	2	1/10th final dose	30 minutes between doses with 1 h observation after last dose
Extremely unlikely	History of headache after penicillin	1	Full dose	1 h observation

[a] Interval and observation may be modified based on patient specific factors and clinician judgment.

Table 15-5 Graded Challenge Protocol for Nonimmediate Maculopapular Exanthems

Dose	Day of Challenge	Observation
1/100th dose	1	1 h[a]
1/10th dose	3–7[b]	1 h[a]
Full dose	6–14[b]	1 h[a]

[a] Depending on patients' reaction and physician judgment, observation can be varied, but patients should be clearly instructed to return for any symptoms for reevaluation.

[b] Interval between dose dependent on history and delay in appearance of rash.

VII. MANAGEMENT AND PREVENTION OF DRUG ALLERGIC REACTIONS

Drugs should be prescribed only for valid indications and combinations of drugs should be used sparingly. This is especially important in individuals who have had multiple reactions to various drugs. Steps to prevent allergic drug reactions include (1) a careful history to determine risk factors, (2) avoidance of cross-reactive drugs, (3) use of predictive tests when available, (4) prudent prescribing of drugs (especially antibiotics) that are frequently associated with adverse reactions, (5) use of oral drugs when possible, and (6) detailed documentation of ADR in the patient's medical record.

A. Acute management of drug reactions

For many drug allergic reactions, simply withdrawing the causative medication may result in resolution of the reaction. Time to resolution of drug reactions varies considerably from hours to days for most, to weeks or even months for other reactions (e.g., DRESS). Depending on the clinical presentation, other management may be required. In patients with suspect SCAR or vasculitis, complete blood counts, liver enzymes, and renal function should be obtained to exclude other organ involvement. Drug-induced anaphylaxis is managed the same as other forms of anaphylaxis and epinephrine should be administered promptly. Antihistamines are

often used for urticaria/angio-edema as well as pruritus from drug reactions. Topical corticosteroids may be helpful for some exanthems. Antihistamines, oral corticosteroids, and NSAIDs may be useful for patients with immune complex reactions to control urticaria, joint symptoms, or vasculitis. Systemic glucocorticosteroids may also be required for the treatment of drug-induced hemolytic, throm-bocytopenic, or granulocytic cytopenias, especially in situations where the responsible drug must be continued as a lifesaving measure.

B. Management of patients with SCAR is different than most other drug allergic reactions. For patients with SJS/TEN, supportive measures including wound care, hydration, nutritional support, monitoring and treatment for infections, and ophthalmologic monitoring are key facets of therapy. Depending on the degree of skin involvement, management in a specialized burn center may be required. The use of systemic corticosteroids in SJS is controversial and is generally avoided in more severe cases such as TEN. Other therapies that have been used include cyclosporine, plas-mapheresis, and high-dose intravenous immunoglobulins (IVIGs). Most studies of IVIG at doses >2 g/kg have demonstrated reduction in mortality associated with TEN. DRESS is often treated with systemic cortico-steroids, especially if there is internal organ involvement, and is usually effective. However, many patients with DRESS recover without therapy, especially with milder syndromes. Other therapies used for DRESS include cyclosporine and IVIG.

C. Management of multiple antibiotic allergy

In patients with multiple antibiotic allergy, infections should be proven by culture (or suggested by radiography) and antibiotics should be avoided for most upper respiratory tract infections such as bronchitis, sinusitis, and otitis media since antibiotic therapy is usually not warranted. Both patients and primary care physicians need to understand that judicious use of antibiotics is key. Testing for penicillin allergy and one or two other classes of antibiotics can be helpful in finding some safe alternatives and reduce the need for induction of drug tolerance procedures. Not all medications need to be tested but enough to develop reasonable therapeutic alternatives. Particularly in patients with numerous medication allergies (e.g., 10 or more) or predominantly subjective symptoms, placebo testing should be considered when doing drug challenges as these individuals have a high rate of reacting to placebos.

D. Induction of drug tolerance

The term **"drug desensitization"** has been widely used and is defined as a procedure that modifies a patient's immune response to a drug, allowing them to take the drug temporarily in a safe manner. In cases such as IgE-mediated drug allergy (e.g., to penicillin), the term drug desensitization is accurate in that patients are indeed sensitized to penicillin prior to the procedure, and afterward typically have diminished or absent skin test reactions, and hence are less sensitive or "desensitized." However, the term "drug desen-sitization" has also been used to describe a number of different protocols for non–IgE-mediated drug allergic patients that in many cases are not truly sensitized initially but may react to the drug through various non–IgE-mediated or even nonimmune mechanisms. Recently, the term "induction of drug tolerance" has been proposed as a more appropriate term to encompass not only IgE-mediated desensitization procedures but other non–IgE-mediated "desensitizations" as well. The term drug tolerance is defined as a state in which a drug-allergic individual will tolerate a drug without an adverse reaction. Drug tolerance does not indicate either a permanent state

of tolerance or that the mechanism involved was immunologic tolerance. Drug desensitizations for IgE-mediated drug allergy are indeed a form of immunologic drug tolerance. Induction of drug tolerance procedures modify a patient's response to a drug (via immunologic or other nonimmunologic mechanisms) to temporarily allow treatment with it safely. Induction of drug tolerance can involve IgE immune mechanisms, non-IgE immune mechanisms, pharmacologic mechanisms, and undefined mechanisms (Table 15-6).

Table 15-6 Classification of Induction of Drug Tolerance Procedures

Mechanism of Drug Reaction	Duration of Procedure	Initial Dose	Potential Mechanism of Drug Tolerance	Examples
Immunologic IgE (drug desensitization)	Hours	µg	Inhibition of internalization of antigen/IgE/FcεRI complex	Penicllin
Immunologic non-IgE	Hours to days	mg	Unknown	Trimethoprim/sulfamethoxazole
Pharmacologic	Hours to days	mg	Metabolic shift, internalization of receptors	Aspirin
Undefined	Days to weeks	µg–mg	Unknown	Allopurinol

All procedures to induce drug tolerance involve administration of incremental doses of the drug but vary considerably over the starting dose and duration of the procedure. Through various mechanisms, these procedures induce a temporary state of tolerance to the drug, which is maintained only as long as the patient continues to take the specific drug. Therefore, this procedure would need to be repeated in the future if a patient requires the drug again, after finishing a prior therapeutic course.

The safety of induction of drug tolerance procedures varies depending on the drug and the protocol used. In the majority of cases of drug desensitizations for penicillin, cancer chemotherapeutics, and monoclonal antibodies, no reactions occur during the desensitization, and severe reactions are uncommon. Induction of drug tolerance procedures may be done in an inpatient or outpatient setting. Supervision will vary depending on the patient, drug reaction, and protocol used but requires a health care provider with knowledge and experience performing these procedures. Specific examples of induction of drug tolerance procedures will be discussed in relation to particular drugs. Appendix VI contains different examples of induction of drug tolerance protocols using oral and intravenous methods.

VIII. DRUG ALLERGY TO SPECIFIC DRUGS

A. Beta-lactam antibiotics

1. *Penicillins*

Approximately 10% of patients may report a history of penicillin allergy, making it one of the most common drug allergies. However, when evaluated, up to 90% of these individuals tolerate penicillin. There are several reasons for this apparent discrepancy. First, many patients may have had adverse reactions that were mistaken for a drug allergy. For example, in childhood, viral exanthems are quite common and may be mistaken for a drug allergic reaction when the rash develops during antibiotic administration. Second, some

patients may have had adverse reactions (e.g., headache) that were neither drug allergic reactions nor even causally related. Finally, the natural history of penicillin allergy is to wane over time. Approximately 30% to 50% of penicillin allergic patients have negative skin tests after 5 years and 80% after 10 years following their reaction. For all of these reasons, the majority of patients with remote histories (>10 years) of penicillin allergy typically tolerate penicillin.

Certainly, not all patients with a history of penicillin allergy need to be evaluated. However, some patients would clearly benefit from an evaluation. Patients with multiple antibiotic allergies who have a significantly limited choice of antibiotics should generally have their penicillin allergy evaluated if they require antibiotics with any regularity. Individuals with known infections that require long-term antibiotics that may lead to development of antibiotic resistance (e.g., vancomycin for methicillin-sensitive *Staphylococcus aureus*) can also be considered for evaluation. Additionally, patients with infections due to organisms in which penicillins may be a preferred therapy should be evaluated.

While penicillin skin testing is used to identify patients with IgE-mediated penicillin allergy, its use is not restricted to only those patients with clear histories of IgE-mediated reactions (e.g., urticaria, angioedema, anaphylaxis). Patients with histories of other cutaneous reactions (e.g., "itchy rash," "measles" rash, unknown history) may also undergo penicillin testing. The reason for this is that patients (and many physicians) are notoriously inaccurate in their description of rashes and one cannot be certain that one of these other rashes was not really urticaria.

There are no absolute contraindications to penicillin skin testing. However, in some patients, penicillin therapy may be contraindicated, regardless of the skin test results. Patients with histories of SCAR due to penicillin should not receive penicillin, regardless of penicillin skin test results. Other less common penicillin drug allergic reactions such as drug-induced fever, hepatitis, hemolytic anemia, and vasculitis are examples where skin testing would not offer useful information as to the safety of reintroducing penicillin.

Penicillin allergens are divided into **major and minor determinants.** The major determinant of penicillin is commercially available as penicilloyl– polylysine (PRE-PEN) in a premixed 6×10^{-5} M solution. Of the minor determinants, penicillin G is commercially available and should be used for skin testing at a concentration of 10,000 units/mL. The other minor determinants (penicilloate and penilloate) have never been commercially available in the United States. Penicillin G left in solution ("aged" penicillin) does not spontaneously degrade to form other minor determinants and therefore cannot be used as a substitute for the other minor determinants.

Penicillin G should be diluted to a concentration of 10,000 U/mL for testing (see Appendix VI). PRE-PEN should be tested without any dilution and is available from ALK-Abello. Initial **penicillin skin testing** should begin with prick–puncture testing with undiluted PRE-PEN and penicillin G 10,000 U/mL along with appropriate positive and negative controls. Since penicillin-allergic individuals rarely react to prick– puncture testing, intradermal (intracutaneous) testing is nearly always required. For intradermal

testing to drugs, injecting a volume sufficient to raise a wheal of approximately 5 × 5 mm is often recommended. It is important to measure the wheal diameter of each intradermal test immediately after it is placed. This testing should be done in duplicate with PRE-PEN and penicillin G but is not necessary for the negative control. Duplicate testing is recommended due to the small changes seen in drug allergy testing and potential for error in interpretation. An intradermal positive control is not required. Serious reactions to penicillin skin testing when performed appropriately are extremely rare.

As opposed to skin testing for inhalants where one typically can see pronounced wheal-and-flare responses, penicillin skin test reactions are often subtle. A criterion for a positive penicillin skin test is a change in diameter of ≥3 mm between the immediate reading and the reading 15 minutes later. A flare response is not required for a positive penicillin skin test. If there is discordance between the duplicate tests, additional testing may be required. A positive reaction to either penicillin reagent is indicative of a positive penicillin skin test.

Penicillin skin testing using both major and minor determinants has been shown to have excellent negative predictive value with approximately 1% to 3% of penicillin skin test–negative patients having immediate reactions. Penicillin skin testing using only PRE-PEN and penicillin G also appears to have a good negative predictive value. The largest study by Green et al. showed that of 346 penicillin skin test– negative subjects, 3.5% had reactions to challenge, with only 25% of those being immediate-type reactions. This is similar to rates of positive challenges from studies using minor determinant mixture in addition to PRE-PEN and penicillin G. Since there is a small risk of reactions in patients who are penicillin skin test negative, a confirmatory penicillin challenge is recommended. In the majority of patients who are being tested, the history is remote and the reaction is nonanaphylactic, and therefore, the pretest likelihood of penicillin allergy is low. For these patients, a full dose of amoxicillin may be used with observation for an hour. Amoxicillin may be used as it covers both penicillin and side chains of aminopenicillins. If they have negative skin tests and a negative challenge, the patient is advised that they may take penicillin in the future if needed. For the rare patient in which the pretest probability for penicillin allergy is high and the skin test is negative, a graded dose challenge to amoxicillin (or penicillin) may be more appropriate. For patients with a positive penicillin skin test, penicillin avoidance is recommended. If penicillin therapy is required, a penicillin desensitization can be performed.

Penicillin skin testing may be performed electively so that the results are available prior to any need for penicillin and therapy is not delayed. The main concern with this approach is resensitization. Several studies have shown that the risk for resensitization to oral courses of penicillin is rare. Therefore, penicillin skin testing does not routinely need to be repeated in patients with a history of penicillin allergy who have tolerated one or more courses of oral penicillin. Data on resensitization after intravenous penicillin are limited but suggest that repeat penicillin skin testing may be considered to exclude resensitization.

Relatively few studies with small numbers of patients have evaluated the specificity

and sensitivity of third-generation ***in vitro*** **assays for detection of penicillin-specific IgE** *in vitro*. These studies demonstrate relatively high specificity but lower sensitivity for penicillin-specific IgE. A US study evaluating a commercial *in vitro* assay for penicillin-specific IgE in patients with a remote history of penicillin allergy found the test lacked utility and offered no advantage over penicillin skin tests. Overall, immunoassays for penicillin-specific IgE antibodies are less sensitive than skin tests, and therefore, skin testing is preferred.

Amoxicillin and ampicillin are associated with delayed maculopap-ular exanthems. These exanthems occur extremely frequently in certain patients, particularly children with infectious mononucleosis. While these reactions are thought to be nonimmunologic, some patients have been shown to have positive delayed intradermal skin tests, though the clinical significance of this is unknown. In Europe, patients with positive skin tests to ampicillin or amoxicillin but with negative penicillin skin tests are frequently reported. These patients are thought to have IgE antibody directed against the R-group side chain. These side chain– specific reactions are infrequently reported in the United States, and there appears to be little value of ampicillin skin testing in the United States. Amoxicillin shares R-group side chains with certain cephalo-sporins, and it is recommended that amoxicillin-allergic patients avoid cefadroxil, cefprozil, and cefatrizine.

2. *Cephalosporins*

Most IgE-mediated reactions to cephalosporins appear to be directed to the R-group side chain, especially the R1 side chain, not the betalactam ring. Patients who had had these reactions to one cephalosporin should avoid other cephalosporins with similar R-group side chains (Table 15-7). The negative predictive value of skin testing to cephalosporins using nonirritating concentrations is unknown, and therefore, a graded challenge is recommended when administering another cephalo-sporin with a dissimilar R side chain to a cephalosporin-allergic patient. The extent of cross-reactivity among cephalosporins for other types of non–IgE-mediated drug allergic reactions is largely unknown.

Table 15-7 Beta-lactam Antibiotics with Identical R-group Side Chains

Identical R Group	Beta-Lactam Antibiotic
R_1	Amoxicillin, cefadroxil, cefprozil, cefatrizine
R_1	Ampicillin, cefaclor, cephalexin, cephradine, cephaloglycin, loracarbef
R_1	Ceftriaxone, cefotaxime, cefpodoxime, cefditoren, ceftizoxime, cefmenoxime
R_1	Cefoxitin, cephaloridine, cephalothin
R_1	Cefamandole, cefonicid
R_1	Ceftazidime, aztreonam
R_2	Cephalexin, cefadroxil, cephradine
R_2	Cefotaxime, cephalothin, cephaloglycin, cephapirin
R_2	Cefuroxime, cefoxitin
R_2	Cefotetan, cefamandole, cefmetazole, cefpiramide
R_2	Cefaclor, loracarbef
R_2	Ceftibuten, ceftizoxime

The risk of reactions to cephalosporins in IgE-mediated penicillin allergic patients appears to be relatively low. Studies of penicillin skin test–positive patients who have been administered cephalosporins show a reaction rate of approximately 3%. The reaction

rate is even lower in those with nonsevere penicillin allergy documented only by history—approximately 0.1%. There is considerable debate regarding the true clinical cross-reactivity of cephalosporins in penicllin-allergic patients, as data suggest this may not be immunologic but rather an inherent propensity of drug-allergic patients to react to other drugs in a nonspecific fashion. For patients with a history of penicillin allergy, if penicillin skin testing is negative, they may receive cephalopsorins and other beta-lactams. When penicillin skin testing is not available, cephalosporins may be given via full dose or graded challenge, depending on the reaction history and likelihood the patient is penicillin allergic.

In patients allergic to cephalosporins, the risk of reacting to other beta-lactams varies. Approximately 75% of cephalosporin skin test– positive patients tolerate penicillin, whereas 97% tolerate aztreonam and 98% to 99% tolerate carbapenems. Skin testing to the alternative beta-lactam followed by a graded challenge of 10% of therapeutic dose followed by full dose 1 hour later has been recommended to evaluate tolerability.

3. ***Aztreonam***

Aztreonam appears to be less immunogenic than other beta-lactams. Penicillin- and cephalosporin-allergic patients may receive aztreonam, with the exception of patients allergic to ceftazidime, which shares an identical R group, who should avoid aztreonam.

4. ***Carbapenems***

There are minimal data on patients with carbapenem allergy. Most studies have focused on cross-reactivity between penicillin and car-bapenems. Retrospective studies of patients with historical reactions to penicillin show a reaction rate to carbapenems from 0% to 11%. In studies of penicillin skin test–positive patients who were administered carbapenems after a negative carbapenem skin test, no patient reacted. Therefore, the approach to carbapenem administration in patients with histories of penicillin allergy is similar to cephalosporins. Penicillin skin test– negative patients should be able to safely receive carbapenems. Skin testing to the carbapenem followed by a graded challenge of 10% of therapeutic dose followed by full dose 1 hour later has been recommended to evaluate tolerability.

B. Non–beta-lactam antibiotics

1. ***Sulfonamides***

Sulfonamides are defined as drugs with an SO_2–NH_2 moiety. Sulfonamide antibiotics are more likely to cause maculopapular exanthems then IgE-mediated reactions. These reactions occur at a higher rate in HIV-positive individuals, and sulfonamide antibiotics are used frequently in HIV patients to prevent *Pneumocystis jiroveci* pneumonia. A number of induction of drug tolerance procedures have been devised to allow safe administration of these drugs in patients allergic to sulfonamide antibiotics. Protocols generally range from hours to days and have high success rates. A few studies have directly compared induction of drug tolerance to full-dose readministration with no difference in success rates. Therefore, these inductions of drug tolerance procedures may not be necessary.

Sulfonamide antibiotics are structurally different than nonantibiotic sulfonamides. Studies have demonstrated no increased risk of reactions to nonantibiotic sulfonamides in

patients with histories of sulfonamide antibiotic allergy.

2. *Vancomycin*

Vancomycin can cause a number of drug allergic reactions including pseudoallergic reactions (red man syndrome), DRESS, linear IgE bullous disease, and rarely IgE-mediated anaphylaxis. Pseudoallergic reactions are common with vancomycin and are related to the rate of infusion. Symptoms include flushing, erythroderma, and pruritus most commonly but may also result in urticaria and even hypotension.

Premedication with antihistamines, avoidance of concomitant opiates, and slowing the rate of infusion is usually effective for these pseudoal-lergic reactions. Induction of drug tolerance protocols have been used when these measures are not successful. In patients with suspected IgE-mediated anaphylaxis, skin testing with nonirritating concentrations (≥10 mg/mL is irritating) may be helpful, and desensitization protocols have been used successfully for these patients as well.

3. *Quinolones*

Allergic reactions to quinolones appear to be increasing. IgE-mediated anaphylaxis and T cell–mediated drug exanthems have been reported. *In vitro* studies suggest a high degree of cross-reactivity among quinolones. Whether this represents true clinical cross-reactivity is less clear. Case reports and small case series suggest that patients allergic to one quinolone may indeed tolerate other quinolones and that skin testing is not predictive of challenge outcomes.

4. *Bacitracin*

Bacitracin is well known to cause contact dermatitis. It can also cause IgE-mediated anaphylaxis and should be considered as a potential allergen in perioperative anaphylaxis.

C. ACE-I

ACE-Is have two major adverse effects—cough and angioedema. Cough occurs more commonly in women, nonsmokers, and Chinese patients. The etiology for ACE-I cough is unclear but may be related to bradykinin, substance P, or other mechanisms. ACE-I cough is typically dry and may be associated with a tickling sensation in the throat. The cough may occur within hours of the first dose or within weeks or months of initiation of therapy. With discontinuation of the ACE-I, the cough usually resolves in 1 to 4 weeks and rarely may linger up to 3 months. Several pharmacologic agents have been reported in small case series to reduce ACE-I coughing including cromolyn, theophylline, NSAIDs, amlodipine, nifedipine, and ferrous sulfate. ACE-I cough is not dose related, and angiotensin II receptor blockers are not associated with an increased incidence of cough.

The incidence of angioedema to ACE-I is estimated to occur in 1 to 7/1,000 patients, and this risk is higher in African Americans compared to whites. ACE-I angioedema is often unrecognized as its manifestation may occur anywhere between a few hours to 10 years after an ACE-I is first taken. A recent retrospective study found a mean of 1.8 years from initiation of ACE inhibitor until the onset of angioedema. ACE-I angioedema accounts for approximately one-third of all cases presenting to the emergency department for angioedema. Characteristically, ACE-I angioedema involves the head and neck primarily, especially the lips and tongue, and rarely may cause concomitant urticaria and pruritus. In some cases, laryngeal edema may cause fatalities. Reports of angioedema of the intestinal tract secondary to ACE-I have also been described. Bradykinin is a prominent mediator in both

hereditary angioedema and ACE-I angioedema. ACE-Is are contra-indicated in patients with hereditary angioedema. In patients with ACE-I angioedema, angiotensin II receptor blockers are often used as alternative medications. Limited data suggest that in patients who developed angio-edema when taking an ACE-I, the risk of developing persistent angioedema when subsequently switched to an angiotensin II receptor blockers is <10%.

Treatment includes discontinuing the medication and careful management of the airway, and in some cases, fresh frozen plasma and the bradykinin B2receptor antagonist (icatibant) has been useful.

D. Aspirin and NSAIDs

Acetylsalicylic acid (ASA) and NSAIDs can cause a spectrum of drug allergic reactions including exacerbation of underlying respiratory diseases, urticaria, angioedema, anaphylaxis, and rarely pneumonitis and meningitis. Some of these drug allergic reactions exhibit cross-reactivity to other NSAIDs and aspirin, while some reactions may be drug specific.

Aspirin-exacerbated respiratory disease (AERD) is a clinical entity characterized by ASA-/NSAID-induced respiratory reactions in patients with underlying chronic respiratory diseases such as asthma, rhinitis, sinusitis, and/or nasal polyposis. AERD affects up to 20% of adult asthmatics, is more common in women, has an average age of onset around the age of 30, and usually starts with rhinitis, progressing to hyperplastic sinusitis and nasal polyposis. Asthma may be present since childhood or may develop de novo, on average 2 years after the onset of nasal congestion and polyposis.

The pathophysiology of AERD is related to excessive production of cysteinyl leukotrienes, elevated numbers of inflammatory cells expressing cysteinyl leukotriene-1 receptors, and greater airway responsiveness to cysteinyl leukotrienes. Within minutes of ingestion of therapeutic doses of ASA or NSAIDs, AERD patients typically have both rhinoconjunctivitis and bronchospasm. The bronchospasm induced may be severe and results in respiratory failure with need for intubation and mechanical ventilation. Gastrointestinal symptoms and urticaria are rare extrapulmonary manifestations of AERD and may be confused with anaphylaxis. Patients with AERD will react to ASA and NSAIDs that inhibit cyclooxygenase-1. Selective cyclooxygenase-2 inhibitors almost never cause reactions in patients with AERD and can typically be taken safely.

There is no diagnostic *in vitro* or skin test for AERD. The diagnosis is usually established by history, but when a definitive diagnosis is required, a controlled oral provocation challenge with ASA may be performed. A recent study showed that 100% of patients with a history of a severe reaction to aspirin (poor response to albuterol with need for medical intervention or hospitalization) had positive oral aspirin challenges, suggesting that the history is usually sufficient to establish a diagnosis. Management of patients with AERD involves avoidance of aspirin and NSAIDs and aggressive medical and/or surgical treatment of underlying asthma and rhinitis/sinusitis. A pharmacologic induction of drug tolerance procedure (a.k.a. aspirin desensitization), during which tolerance to aspirin can be induced over a few days and then maintained chronically, is an important therapeutic option for patients with AERD and improves clinical outcomes for both upper and lower respiratory tract disease (see Appendix VI).

Several other drug allergic reactions to ASA or NSAIDs may occur. Patients with chronic urticaria/angioedema may have exacerbation of their urticaria/angioedema with ingestion of NSAIDs that inhibit cyclooxygenase-1 but typically tolerate cyclooxygenase-2 inhibitors. Patients without a history of underlying chronic urticaria/angioedema may develop acute urticaria/angioedema with

ingestion of aspirin or NSAIDs. Some of these patients demonstrate cross-reactivity to other cyclooxygenase-1

inhibitors, while others have selective reactions to a particular NSAID. Drug challenges are required in these individuals to determine if cross-reactivity to other NSAIDs exist. Anaphylactic reactions to NSAIDs are typically drug specific, and these patients typically tolerate other NSAIDs. Finally, some patients are not easily categorized who have blended reactions with overlap of various clinical features from the above well-described ASA/ NSAID reaction syndromes.

Patients with aspirin allergy who require aspirin for cardiovascular diseases are a special management issue. There are limited reports of rapid "desensitization/graded challenges" (2 to 5 hour) protocols in patients with histories predominantly of cutaneous reactions (urticaria/angioedema) to aspirin but also including a few patients with histories of respiratory reactions. While generally successful for the majority of patients, even those with respiratory reactions, patients with chronic urticaria/angioedema that is exacerbated by aspirin may not achieve tolerance via either rapid (2 to 5 hours) or standard (2 to 4 days) aspirin challenge/desensitization protocols. It is unclear whether these protocols truly induce drug tolerance (desensitization) or are simply a multistepped graded dose challenge. An example of a rapid desensitization/graded challenge protocol for aspirin is in Appendix VI.

E. Radiocontrast media

RCM are highly concentrated solutions of triiodinated benzene derivatives. RCM are available as ionic and nonionic compounds, the latter being associated with less adverse reactions. Mild immediate reactions to RCM occur in 4% to 13% of patients receiving intravenous nonionic monomers and 1% to 3% of patients receiving nonionic RCM. Severe immediate reactions are reported in 0.1% to 0.4% of patients receiving intravenous non-ionic monomers and 0.02% to 0.04% of patients receiving nonionic RCM. Drug allergic reactions to oral contrast are rare. A number of risk factors have been associated with RCM reactions including prior RCM reactions, female gender, asthma, cardiovascular disease, and beta blocker exposure.

Nonspecific mild reactions are relatively common, with a sensation of warmth or nausea. Symptoms of immediate reactions range from pruritus, rhinitis, and urticaria to hypotensive anaphylactic reactions. The majority of immediate reactions occur within 5 minutes of the injection. Nonimmediate reactions to RCM may also occur hours to days after RCM administration. A number of cutaneous manifestations of delayed RCM reactions have been reported. A maculopapular exanthem is most common, but urticaria, angioedema, erythema multiforme, and SCAR have all been reported after RCM administration.

The mechanisms of immediate RCM reactions remain a subject of debate. Traditionally, these reactions are thought to be pseudoallergic reactions due to direct mast cell activation from high osmolal RCM, activation of the complement system, or bradykinin activation. Recent studies from Europe suggest that some patients with immediate reactions may have positive skin tests to nonirritating doses of RCM suggesting that some patients may have an IgE-mediated mechanism. Further large-scale studies are required to validate these observations, and at present, the value of skin testing with RCM in the evaluation and management of these patients is unclear. Mechanisms for delayed RCM reactions appear to be T cell–mediated with

positive delayed intradermal tests or patch tests. Recommendations for skin testing to RCM are to perform prick testing with undiluted RCM and intradermal testing with a 1:10 dilution. For delayed

RCM reactions, intradermal tests should be read at 48 and 72 hours.

1. Prevention of immediate RCM reactions

In patients with prior immediate reactions to RCM who are in need of RCM, several steps are required to reduce the risk: (1) determine if the contrast study is essential; (2) discuss the risk with the patient; (3) ensure proper hydration; (4) use a nonionic, iso-osmolar RCM and preferably a different RCM agent than the culprit RCM; and (5) use an established premedication regimen. A typical pretreatment regimen consists of prednisone 50 mg 13, 7, and 1 hours before the procedure and diphenhydramine 50 mg 1 hour before the procedure. The addition of ephedrine 25 mg or albuterol 4 mg 1 hour to the procedure may also be considered but should be balanced against risk in patients with cardiovascular disease. The use of H_2 antagonists in the pretreatment regimen is controversial because it may increase the RCM reaction rate. It should be noted that premedication does not eliminate the possibility of a reaction and that severe reactions may still occur.

2. Prevention of delayed RCM reactions

Data are very limited in regard to prevention of delayed RCM reactions. Performing delayed intradermal testing to different RCMs may be helpful, but since the negative predictive value is unknown, patients may still react. Corticosteroid with or without cyclosporine has been used as pretreatment, but it is unclear how efficacious these approaches are.

3. Gadolinium reactions

Drug allergic reactions to gadolinium occur less frequently than with RCM, with fatal reactions reported to be <1 in 1 million. Premedication with corticosteroids and antihistamines has been utilized for drug allergic reactions, but breakthroughs have been reported and the true efficacy of this approach is unknown. Nephrogenic systemic fibrosis is a devastating complication of gadolinium agents in patients with renal dysfunction. Screening for renal function prior to gadolinium use has markedly reduced these reactions.

F. Local anesthetics

IgE-mediated reactions to local anesthetics are extremely rare, yet many patients are labeled allergic to all “caines” and denied access to these drugs. Most adverse reactions to local anesthetics are due to nonallergic factors such as vasovagal responses, toxic or idiosyncratic reactions due to inadvertent intravenous epinephrine, or anxiety. Local anesthetics are grouped into benzoate esters and amides. Based on patch testing, there is cross- reactivity among the benzoate esters (which do not cross-react with amides) but not among the amides. It is not known what, if any, relevance this has on immediate-type reactions to local anesthetics. If the reaction history is consistent with a possible type I reaction, skin testing followed by graded challenge tests may be performed using the same (epinephrine-free) local anesthetic that is intended to be used. While there are differences in reported graded challenge procedures, a rapid and convenient protocol is as follows (see Appendix VI): Prick skin tests are first performed with the undiluted anesthetic. If this is negative after 20 minutes, an intradermal test is performed using 0.04 mL of 1:100 dilution of local anesthetic. If negative after 20 minutes, a 1.0-mL subcutaneous injection of saline as a placebo is administered. If no reaction after 20 minutes, 1.0 mL of local anesthetic is administered and the patient observed for 20 minutes. Placebo administration is often important in testing patients as they often react due to anxiety

regarding the test. False-positive intracutaneous tests may occur in some patients. Also, very rare patients may have positive skin tests to methylparabens in local anesthetics, and some of these may be false positive. In these situations, preservative-free local anesthetic should be used for skin testing/graded challenge.

G. Cancer chemotherapeutics

Drug allergic reactions have been reported for most chemotherapeutic agents with a wide spectrum of reactions and severity. In some cases, it is the excipient that can cause the reaction. Cremophor EL is a nonionic emulsifier capable of activating complement, which can cause anaphylactoid reactions.

1. In the **taxane** family, paclitaxel and docetaxel have a high frequency of causing first-dose anaphylactoid reactions. Pretreatment with corticosteroids and antihistamines is effective at reducing the rate of these reactions to approximately 2% to 4%. A suggested premedication regimen includes dexamethasone 20 mg (oral or intravenous), 12 and 6 hours before dosing, and diphenhydramine 50 mg and cimetidine 300 mg or ranitidine 50 mg, both administered intravenously 30 minutes before treatment. Patients who react despite premedication can undergo an induction of drug tolerance procedure.
2. **Platinum-based compounds** such as carboplatin and oxaliplatin are associated with IgE-mediated reactions. Unlike taxanes, there is a period of sensitization required, and thus, reactions are rare before the first four cycles but the rate progressively increases with many reacting at the eighth cycle. Skin testing appears to have fairly good negative predictive value in screening patients for allergic reactions. Skin testing has been shown to be positive in most patients who have had symptoms within 2 hours of receiving the platinum agent. Prick and intradermal testing diluted from 10^{-1} to 10^{-3} has been recommended as a diagnostic tool in those patients who have experienced allergic reactions to platinum salts. For patients with positive skin tests in need of continued therapy, desensitization protocols have been used successfully (see Appendix VI).
3. **Asparaginase** is another chemotherapeutic agent with a high frequency of drug allergic reactions in up to 35% of treated patients. The mechanism of these reactions is unclear, with both IgE-mediated and complement activation being proposed mechanisms. Intradermal skin testing with 0.1 mL of a 20-IU/mL concentration has been suggested, but false positives and false negatives have occurred. Most patients who react to *Escherichia coli*–derived l-asparaginase may tolerate *Erwinia*-derived l-asparaginase; however, cross-reactivity can also occur. Desensitization has been used successfully.
4. **Etoposide and teniposide** are antimitotic agents that may cause drug allergic reactions in 6% to 51% including anaphylaxis. The mechanism is unclear with both immunologic and nonimmunologic mechanisms proposed. Teniposide is dissolved in the solvent Cremophor EL (similar to paclitaxel), and some reactions may be due to Cremophor EL. Patients with drug allergic reactions have been successfully rechallenged with slower infusion rates and premedication using antihistamines and corticosteroids, but as many as one-third still had reactions. In patients reacting to etoposide, changing to etoposide phosphate may be tolerated.

H. Corticosteroids

Allergic contact dermatitis to topical corticosteroids is the most common type of allergic

reaction to corticosteroids. Systemic allergic reactions to corticosteroids are rare, occurring in approximately 0.1% of doses, and anaphylactic reactions are well described. While the mechanism is unclear, evidence is suggestive that IgE-mediated reactions may occur, possibly to a hapten complex. A recent study of 15 patients found that intradermal skin tests using dilutions of 1:1,000, 1:100, 1:10, and full strength were positive in all patients who reacted to a steroid with a parenteral formulation. Skin prick tests to prednisone and prednisolone were not helpful. Ninety percent of patients tolerated a challenge to a corticosteroid with a negative skin test. Some patients may react to more than one corticosteroid preparation, but there does not appear to be a clear pattern of cross-reactivity.

I. Heparin

Heparin is a rare cause of allergic reactions that may manifest as thrombocytopenia, cutaneous reactions, or anaphylaxis. Heparin-induced thrombocytopenia type I causes mild thrombocytopenia due to platelet aggregation, occurs early in the course of therapy, and resolves spontaneously. Heparin-induced thrombocytopenia type 2 is an immunologic reaction due to antibodies against platelet factor 4, which binds to heparin, resulting in immune complex formation and more severe thrombocytopenia and risk for thrombosis. Testing for platelet factor 4 antibodies and heparin-induced platelet activation assays are useful in confirming a diagnosis.

Cutaneous reactions to heparin are usually manifestations of DTH responses. Eczematous injection site lesions are most common; however, more generalized papules may also occur. Lesions usually occur in 7 to 10 days. The majority of patients will have positive delayed intradermal skin tests and using undiluted or 1:10 dilution of heparin. Testing is recommended to be read at least 4 days afterward. Most of these patients will tolerate intravenous forms of heparin. Cross-reactivity does exist for heparinoids or fondaparinux. Thrombin inhibitors are typically considered safe alternatives.

Heparin-induced anaphylaxis is rare. IgE-mediated reactions have been reported along with successful desensitizations. A recent outbreak of ana-phylactic reactions to heparin in the United States and Germany was attributed to a contaminant in heparin lots, an oversulfated form of chondroitin sulfate. This oversulfated chondroitin sulfate contaminant has been shown to cause activation of the kinin–kallikrein pathway with generation of bradykinin. Clinically, reactions to contaminated heparin products were associated with hypotension and abdominal pain, and variably angioedema, but typically lacked urticaria and pruritus.

J. Insulin

Insulin including human insulin can cause a variety of different immunologic drug reactions. Localized injection site reactions are the most common and may often be IgE mediated. IgE-mediated anaphylaxis may also rarely occur. In cases of immediate reactions to insulin, skin testing is typically

positive, often with undiluted prick testing. Intradermal testing may be performed using different insulin preparations with 10-fold dilutions (starting dilution based on reaction severity) up to 1:10 dilution. Specific IgE testing to insulin may also be helpful. IgE-mediated protamine allergy may be mistaken for insulin allergy. The optimal concentration for protamine skin testing is unclear but may be <30 mg/mL.

Desensitization has been successful in insulin allergy. Case reports exist of patients who were

intolerant of subcutaneous insulin but were tolerant of intravenous insulin.

K. Perioperative agents

Anaphylactic reactions to agents used during general anesthesia may occur in as many as 1 in 2,100 operations. Etiologic agents are numerous and include but are not limited to neuromuscular blocking agents, antibiotics, opiates, latex, hypnotics, colloids, and blue dyes. Women are at higher risk for reactions, and many patients react with first exposure. Exposure to cross-reacting substances such as cosmetics has been proposed, but other unidentified substances that lead to cross-reactive IgE sensitization are possible.

Skin testing has been reported to be of diagnostic utility in identifying the causative agent in cases of anaphylaxis during general anesthesia. Skin testing has not been applied to any "gold standard" for anesthetic allergy due to the inherent dangers with challenging a patient with a history of anaphylaxis as well as the inherent pharmacologic effects of the anesthetic. When skin testing is used to guide subsequent anesthetic agents, the risk of recurrent anaphylaxis to anesthesia is low. Nevertheless, false-negative skin tests have been reported and the true-negative predictive value remains unknown.

The concentrations and dilutions for skin testing used in different studies are varied. The best-studied approach is recommended by the French Society of Anesthesiology and was used in a study of 789 patients being evaluated for allergic reactions to anesthetics. It uses a combination of prick and intradermal tests. The drugs tested in this study included neuromuscular blocking agents, antibiotics, hypnotics (propofol, thiopental, midazolam), opioids, and others. Prick tests are performed with undiluted drug, with the exception of atracurium, mivacurium, and morphine, which are tested using a 1:10 dilution. Intradermal tests are performed with 0.02 to 0.05 mL of serial dilutions of the drug every 15 minutes. The initial dilution is 10^{-3} when the prick test is negative, and subsequent intradermal tests are performed at 10-fold higher concentrations up to 1:10 dilution for most drugs. The final testing dilution for morphine, rocuronium, and cisatracurium is 1:100, and, for atracurium and mivacurium, a maximal dilution of 1:1,000 is recommended. Specific IgE tests for detecting sensitization to neuromuscular blocking agents and latex have also been used but may not be as sensitive as skin testing (especially for neuromuscular blocking agents).

L. Biologic agents

In the past decade, a number of different biologic immune modulatory agents have been developed to treat various inflammatory diseases and malignancies. These agents differ from other drugs in that they are not small-molecular-weight compounds but large potentially immunogenic

proteins and they all have inherent immunologic effects. Because of all of these differences, a separate type of classification for adverse reactions to biologic agents has been proposed based on the mechanism of reactions. High-dose reactions are related to high cytokine levels administered directly or from cytokines released (e.g., capillary leak syndrome). Hypersensitivity reactions may be either antibody or cell mediated. Immune or cytokine dysregulation may result in secondary immunodeficiency, autoimmunity or allergic/atopic disorders. Cross-reactive reactions may occur when the biologic agent is intended for a pathologic cell type but cross-reacts with indent cells. Finally, biologics may also result in nonimmunologic side effects.

Capillary (vascular) leak syndrome is a rare but potentially fatal condition that has been attributed to a number of biologic agents including interleukin-2, granulocyte macrophage colony-stimulating factor, and G-CSF. Clinical and biochemical findings may include fever, edema

(peripheral, pulmonary, ascites, pleural/pericardial effusions), weight gain, hypotension, hypoalbuminemia, and multiorgan failure. The mechanism of the endothelial damage with subsequent fluid and protein extravasation is unclear but appears to be related to the inherent biologic effects of these cytokines.

Tumor necrosis factor-α antagonists include humanized and fully human monoclonal antibodies to TNF-a (infliximab, adalimumab, golim-umab, certolizumab) and TNF-receptor fusion proteins (etanercept). Acute infusion reactions are a relatively common adverse reaction to infliximab often after the first dose, usually occurring within 4 hours of the infusion and characterized by symptoms including hypotension/hypertension, chest pain, dyspnea, fever, and urticaria/angioedema. The pathophysiology of these reactions is not known but is usually not IgE-mediated, though several cases of anaphylaxis have been reported. The majority of patients can continue the infusion with reduction in rate or with premedication. Delayed serum sickness–like reactions with symptoms of fever, urticaria/ angioedema, and myalgias have also been reported but are much less common. The presence of antibodies to infliximab has correlated with both acute and delayed infusion reactions to infliximab. Etanercept and, less commonly, adalimumab are associated with delayed injection site reactions that typically peak at 2 days, usually occur in the first 2 months of therapy, and rarely cause discontinuation of treatment. Recall injection site reactions at the sites of previous injections may also occur and may be T cell–mediated delayed-type hypersensitivity reactions. In addition to the above-mentioned infusion or injection related reactions, a number of other immunologic adverse reactions have been reported with TNF-a antagonists including vasculitis, systemic lupus erythematosus, psoriasis, ILD, ocular autoimmune diseases, sarcoidosis, and hepatitis. A recent Cochrane meta-analysis indicated that infliximab and adalimumab were associated with higher total adverse events while certolizumab pegol was associated with a significantly higher risk of serious infection.

Anaphylactic reactions have been reported with several monoclonal antibodies including infliximab, basiliximab, muromonab, omalizumab, and cetuximab. Cetuximab anaphylaxis was discovered to be due to preexisting antibodies to an oligosaccharide, galactose-a-1,3-galactose present on the Fab portion of cetuximab. Sensitization to galactose-a-1,3-galactose has been shown to occur from tick bites from *Amblyomma americanum*.

Anaphylactic reactions have been reported with **omalizumab** in <0.1% of treated patients. Most but clearly not all anaphylactic reactions occur to the first three doses and within 2 hours of the injection. It remains unclear as to whether omalizumab reactions are due to IgE against omalizumab, an excipient, or a non–IgE-mediated mechanism. Intradermal testing of omal-izumab using saline as a diluent appears to be nonirritating at 1:100,000 dilution. Rare case reports exist using procedures to induce drug tolerance to omalizumab and are not universally successful with one case of anaphylaxis reported from an attempted induction of drug tolerance procedure. Therefore, these procedures should be approached with extreme caution.

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16

Allergic and Nonallergic Reactions to Food

Stephen R. Boden and A. Wesley Burks

I. ALLERGIC AND NONALLERGIC FOOD REACTIONS

The term "food allergy" has often been used to denote any adverse reaction after ingestion of a food. This broad definition has come to encompass both hypersensitivity and intolerance reactions to food proteins. While these reactions each occur after the ingestion of food, the processes involved are unique and not interchangeable.

A. Food intolerance

Food intolerance describes an atypical reaction following the ingestion of a food or food additive. This reaction is not mediated by the immune system and may be caused by any number of factors. For example, Scombroid fish poisoning or toxins secreted by bacteria such as *Salmonella, Shigella,* or enterotoxin-producing *Escherichia coli* may result in gastrointestinal (GI) symptoms following ingestion of contaminated food. Metabolic abnormalities such as those seen with lactose intolerance may contribute to food intolerance. Pharmacologically active components of food, like caffeine, may also elicit adverse reactions.

B. Food hypersensitivity

Food hypersensitivity results from the sensitization to a specific food protein and may develop after exposure to small amounts of food protein. Most physicians associate food hypersensitivity with immunoglobulin E (IgE)-mediated anaphylaxis, although non–IgE-mediated reactions also occur. In IgE-mediated food allergy, the patient develops specific IgE directed against a portion of the food protein. This food-specific IgE is then bound to high-affinity receptors found on tissue mast cells and basophils. Upon reexposure to the food, IgE molecules bound to these high-affinity receptors are cross-linked and trigger the release of preformed mediators (i.e., histamine and tryptase) as well as induce mediator synthesis (i.e., leukotrienes and prostaglandins), leading to anaphylaxis. Although IgE-mediated (type I) reactions are well characterized and account for the majority of food hypersensitivity, non–IgE-mediated immune responses are thought to play a role in several disease processes. Both IgE- and non–IgE-mediated diseases will be discussed in this chapter.

C. Epidemiology

Establishing an accurate incidence for food reactions has proven difficult for several reasons. As discussed above, the lack of a universally applied definition for food allergy may lead to inappropriate inclusion or exclusion of a reaction. Additionally, many food reactions are not reported to the health care system when symptoms are mild or are not recognized. Published studies indicate that self-reported incidence of food allergy overestimates the actual incidence in the population. In one study, 12% of children and 13% of adults reported having an allergy to food, while only 3% of all ages were found to have a positive history of food reaction

accompanied by objective findings with an oral food challenge, skin prick test (SPT), or *in vitro* food-specific IgE testing. Current studies estimate the prevalence of specific food allergy in the population at 0.9% allergic to milk, 0.3% allergic to egg, 0.75% allergic to peanut, 0.3% allergic to fish, and 0.6% allergic to shellfish.

II. IgE-MEDIATED DISEASE

Food hypersensitivity mediated by IgE may affect multiple organ systems, and not every organ system need to be involved with each episode. The signs and symptoms of IgE-mediated reactions may be found in the chapter on anaphylaxis.

III. POLLEN-ASSOCIATED FOOD ALLERGY SYNDROME

Pollen-associated food allergy syndrome, also called oral allergy syndrome, is confined almost exclusively to the oropharynx, rarely involving other organ systems. Associated with the ingestion of fresh fruits or vegetables, symptoms arise quickly after exposure and are generally self-limiting. Common symptoms include itching and/or swelling of the lips, tongue, soft palate, and the throat. Symptoms are the result of IgE cross-reactivity between food proteins and wind-borne pollen. Ragweed and birch pollen are frequently identified. Exposure to cooked or preserved fruits and vegetables does not provoke symptoms, suggesting a conformational change alters IgE binding and mast cell activation. Table 16-1 provides a list of common foods and the pollen that may trigger these symptoms.

Table 16-1 Food–Pollen Allergen Cross-Reactivity

Common Plant Pollen Allergen	Cross-Reactive Fresh Foods
Birch	• Apple • Cherry • Pear • Hazelnut • Celery • Carrot • Soybean • Potato • Tomato • Peanut
Ragweed	• Melon • Banana • Kiwi

IV. FOOD-INDUCED ANAPHYLAXIS

Food-induced anaphylaxis, commonly called food allergy, typically occurs within 2 hours of eating the trigger food. Up to 80% of patients will experience cutaneous symptoms. Acute urticaria or angioedema is seen most commonly. The absence of skin symptoms can lead to failure to diagnose anaphylaxis. Respiratory symptoms include edema of the nasal mucosa, congestion, nasal and/or ocular pruritus, tearing, rhinorrhea, and sneezing. The lower airway may also be involved with cough, voice changes, or wheezing. When affecting the GI tract, anaphylaxis may cause nausea, vomiting, abdominal pain or cramping, and diarrhea. The percentage of patients experiencing symptoms may be found in the chapter on anaphylaxis. Symptoms usually develop suddenly and may progress quickly without intervention. Recognition of anaphylaxis and rapid

treatment, as discussed elsewhere, is essential for patient safety. Although any food may trigger an anaphylactic reaction, most are caused by a small number of foods. Ninety percent of food-induced anaphylaxis in children is triggered by cow's milk, hen's egg, peanut, tree nut, soy, wheat, or fish. In adults, this list includes shellfish as well. Fatal food anaphylaxis is seen most often in adolescents with a known food allergy who fail to receive injectable epinephrine in a timely manner. A history of asthma or of a prior severe food reaction also increases the risk of fatal food anaphylaxis. The natural history of food allergy is currently under investigation. Published results at this time indicate that up to 80% of children with allergy to milk and egg will develop tolerance between 5 and 16 years of age. Contrastingly, only about 20% of children with peanut allergy will develop tolerance in the same time period. Allergies developed in adults also are more likely to persist even with strict avoidance. The mechanism by which tolerance develops is still unknown; however, those who do develop tolerance tend to have lower food-specific IgE at the time of diagnosis. It should be noted that the severity of food allergy reactions has not been correlated with size of SPT, level of specific IgE, or amount ingested resulting in allergic reaction. Cross-reaction seen in IgE testing between similar foods has been demonstrated, for example, legumes (i.e., peanut and soy) and milk (i.e., cow's milk and goat's milk). Table 16-2 lists several foods that may cross-react within a family and the likelihood of clinical significance.

Table 16-2 Food Allergen Cross-Reactivity

	Specific IgE to Multiple Members of the Food Family	Clinical Reactivity
Milk (cow, goat milk)	Common	Common
Legumes (peanut, soy, green pea)	Common	Uncommon
Wheat	Common	Uncommon
Fish	Common	Uncommon
Tree nuts (walnut/pecan, pistachio/cashew)	Common	Uncommon
Egg–chicken	Occasional	Rare
Beef–milk	Occasional	Uncommon
Crustacea–mollusks	Common	Unknown

V. ATOPIC DERMATITIS

Atopic dermatitis is a chronic skin disorder that generally begins in early infancy and is characterized by typical distribution, extreme pruritus, chronically relapsing course, and association with asthma and allergic rhinitis. The disruption of the skin barrier may allow for increased sensitization, and most children will present with specific IgE to foods already tolerated in the diet. In well-controlled studies, about one-third of children with atopic dermatitis have food allergic reactions. As will be discussed below, a detailed dietary history may assist differentiation between sensitization and allergy.

VI. MIXED IgE-, NON–IgE-MEDIATED DISEASE

A. Eosinophilic esophagitis

Eosinophilic esophagitis (EoE) usually presents in childhood but has been seen increasingly in adults as well. Patients typically complain of vomiting, retrocardiac pain, and abdominal pain.

Dysphagia is a common complaint, and food impaction has been observed in adults with EoE. Up to 70% of patients demonstrate food-specific IgE without symptoms of immediate food hypersensitivity. In addition to IgE production, expression of serum cytokines and inflammatory markers including COX-2, periostin, IL-5, IL-13, and eotaxin-3 attracts inflammatory lymphocytes and eosinophils. Current consensus requires an esophageal biopsy with the presence of >15 eosinophilic cells per high-powered field for diagnosis. Endoscopic evaluation may reveal longitudinal furrows, concentric rings, white exudates, mucosal edema, or esophageal narrowing, which are suggestive but not diagnostic of EoE disease. Resolution of symptoms and histologic changes following acid suppression with a proton pump–inhibiting medication may be seen in patients with gastroesophageal reflux disease but not with EoE. Dietary therapy in children has shown some effectiveness when trigger foods are avoided. Strict elimination diets using amino acid–based formulas appear superior to food elimination based either on specific IgE testing or elimination of common food allergens. Repeat endoscopy is necessary to document resolution of tissue eosinophilia after elimination diet. Endoscopy may also be used following reintroduction of food to assess recurrence of EoE disease.

B. Non–IgE-mediated disease

The pathophysiology of non–IgE-mediated food hypersensitivity remains incomplete. The clinical presentation and history remains the key to diagnosis, with limited laboratory tests for confirmation. We discuss three of the more common presentations below.

C. Food protein–induced enterocolitis syndrome

Food protein–induced enterocolitis syndrome (FPIES) is a relatively rare disorder of the GI tract identified in the pediatric patient. A recent study of 13,019 Israeli infants found an incidence of 0.34% (44/13,019), all with symptoms before 6 months of age. Milk or soy formula has been implicated in several cohorts; however, none of the Israeli infants reacted to either milk or soy. FPIES is thought to develop after stimulation of T cells by food protein, although the role of T cells in the disease remains unclear. Endoscopic biopsy specimens may demonstrate patchy villous injury with prominent eosinophilic infiltration and colitis. Delayed onset of symptoms and lack of cutaneous manifestations often delays the diagnosis, subjecting children to repeated episodes, unnecessary testing, and occasionally invasive procedures. Fortunately, the diagnosis may be made clinically, and endoscopy is rarely indicated. The child classically presents at 3 to 7 months of age with profound vomiting about 2 hours after ingestion of an offending food protein, with or without diarrhea. Children may appear pale, cyanotic, or lethargic. Patients may present with a metabolic acidosis. Symptoms occur after each exposure to the triggering food. SPT and serum IgE to specific foods are negative. Rice has been the most commonly implicated solid food. Other triggering foods reported include wheat, oat, sweet potato, and banana. Avoidance of the triggering food protein leads to rapid resolution of symptoms. After 2 weeks of avoidance, an open feeding challenge may confirm the diagnosis. Caution during food challenges is warranted as some children experience more significant reactions after a period of avoidance. Treatment consists of complete avoidance of the triggering food, and tolerance develops in most children by 3 to 4 years of age.

D. Allergic proctocolitis

Presenting in the first weeks to months of life, infants with allergic proctocolitis demonstrate

normal development and weight gain but pass stools containing gross blood with or without mucus. As many as 60% of these infants are breast-fed, the remaining children receiving either cow's milk or soy-based formula. The incidence of allergic proctocolitis has yet to be established; however, in one study of 22 infants with rectal bleeding, 14 (64%) were found to have allergic colitis on rectal biopsy. In cases where the diagnosis was in question, pathologic evaluation of tissue samples reveals an eosinophilic infiltration of the epithelium, lamina propria, and the muscularis of the distal colon, though biopsy is not recommended to establish the diagnosis. The elimination of milk or soy protein from the diet, either through maternal diet modification or use of a hydrolyzed infant formula, leads to resolution of symptoms within 24 to 72 hours. Specific IgE to milk or soy protein is typically not found in these infants. Most cases can be diagnosed with history and elimination diets, as with FPIES. After resolution of symptoms following an elimination diet, most children are able to tolerate a normal diet by 12 to 24 months of age.

E. Celiac disease

Celiac disease is an autoimmune disorder primarily affecting the GI tract of susceptible individuals with an incidence estimated at 1% of the population. There is a strong genetic predisposition among patients with HLA-DQ2 and HLA-DQ8, imparting an increased risk of disease. Dietary proteins, known as glutens, found in wheat, rye, and barley, trigger an immune response in susceptible patients. Tissue transglutaminase (tTG) deamidation of gluten produces peptides well suited for presentation by HLA-DQ2 and HLA-DQ8. Peptide presentation to CD4+ lymphocytes in turn stimulates antigluten and anti-tTG B-cell immunoglobulin A (IgA) directed against gluten and tTG. In addition to immunoglobulin production, the presentation of gluten products stimulates the activity of intraepithelial natural killer cells, leading to damage of the intestinal epithelium and villous atrophy. Patients may present with diarrhea, bloating, abdominal pain, and cramping. Malabsorption from untreated disease may lead to vitamin deficiency, osteoporosis, and failure to thrive. Serum detection of IgA against tTG suggests the need for endoscopic biopsy for confirmation of the diagnosis. The villous atrophy is reversible with strict avoidance of gluten from the diet. As with IgE-mediated food allergy, the only therapy currently available for treating celiac disease is avoidance of gluten-containing foods. Table 16-3 provides a list of foods that must be avoided in celiac disease.

Table 16-3 Foods to Avoid in Celiac Disease

Grains to avoid in all forms	• Wheat (all forms)
	  • Durum
	  • Graham
	  • Kamut
	  • Semolina
	  • Spelt
	• Rye
	• Barley (malt, malt flavoring)
	• Triticale (a wheat/rye hybrid)

Grains and flours that may be consumed (uncontaminated sources)	• Rice • Corn • Oat • Soy • Potato • Tapioca • Beans • Garfava flour • Sorghum • Quinoa • Millet • Buckwheat • Arrowroot • Amaranth • Teff • Nut flours

VII. NON–IMMUNE-MEDIATED DISEASE

A. Lactose intolerance

Lactose intolerance is often misidentified as an allergic disease. Lactose is a disaccharide carbohydrate found primarily in milk and must be hydrolyzed prior to absorption by the intestinal tract. Lactase, a β-galactosidase found at the tips of the intestinal villi of the jejunum, reduces lactose to its component glucose and galactose molecules that are then absorbed. Lactose that is not digested passes to the colon where resident bacterial flora fermentation leads to the symptoms of gas, bloating, and diarrhea. Evaluation of stool for reducing substances may aid in diagnosing lactose intolerance. Elimination of lactose from the diet with resolution of symptoms that return on rein-troduction of lactose also points to abnormalities in lactose digestion. The hydrogen breath test is another noninvasive tool for the diagnosis of lactose intolerance. Hydrogen produced during lactose fermentation is absorbed in the blood stream and exhaled by the lungs. Measuring an increase in hydrogen exhaled following a lactose challenge is useful in diagnosing lactose intolerance without invasive biopsy.

B. Toxic reactions

Scombroid fish poisoning may be confused with immune-mediated anaphylaxis. Improper handling of fish allows bacterial decarboxylation of free amino acids (i.e., histidine) found naturally within the flesh. Fish with high levels of free histidine such as tuna, mackerel, mahi-mahi, and sardines have been implicated. The ingestion of fish containing more than 100 mg of histamine per 100 g may result in symptoms similar to those seen with native histamine release, including flushing, hives, pruritus, or respiratory or GI symptoms.

C. Food additives and preservatives

Food additives are frequently suspected triggers of reactions. Food additives and preservatives usually involve non–IgE-mediated reactions. One suggested mechanism is that

sulfites produce hydrogen sulfite gas that exacerbates the preexisting asthma disease. While the mechanism of action is not fully understood, some asthma patients have experienced exacerbation of symptoms following ingestion of high–sulfite-containing wine. A recent double-blind challenge study of 26 atopic adults with eczema or asthma found no worsening of cutaneous or respiratory symptoms after ingestion of the yellow dye tartrazine (FD&C yellow 5). In guidelines for the diagnosis and management of food allergies published in 2010, the expert panel recommendations indicate that currently there is insufficient evidence to support allergy testing to food additives or preservatives.

VIII. DIAGNOSIS

As with any medical condition, the evaluation of suspected food reaction starts with a detailed history and physical examination. Table 16-4 provides a list of differential diagnoses to consider when evaluating food reactions. The key aspects of the history should include the following: the type and quantity of the food suspected of triggering the reaction; the time between ingestion of the food and the onset of symptoms; a thorough list of symptoms (i.e., cutaneous, respiratory, or GI); whether similar symptoms develop with subsequent exposure to the suspected food; whether other activities, such as exercise, are associated with the episode; and the length of time since the last episode. While history alone is insufficient to diagnose food allergy, it will focus the diagnostic investigation.

Table 16-4 Differential Diagnosis

1. IgE-mediated food allergy
2. Disaccharidase deficiency
3. Celiac disease
4. Gastrointestinal disorder
   a. Vomiting
   b. Diarrhea
   c. Irritable bowel disease
   d. Eosinophilic esophagitis
5. Food poisoning
   a. Bacterial contamination
   b. Histamine toxicity
6. Systemic mastocytosis
7. Hereditary angioedema
8. Reaction to food additives
   a. Yellow dye #5 known to cause hives
   b. Monosodium glutamate ingested in large amounts may induce transient flushing, warmth, headaches, facial pressure, and chest pain
   c. Sulfites may exacerbate asthma symptoms

A. Dietary history

An accurate, detailed dietary history is the first step to establishing a link between a food and symptoms of allergy or intolerance. The diet history may be kept in a simple notebook. While it may not provide new insight to the patient symptoms, this history can record the temporal relationship between the suspected food and the onset of symptoms. The dietary history, together with elimination diets, may be especially helpful when symptoms fail to improve during the elimination of the suspected food. For an elimination diet, often the first step in evaluating a suspected trigger, foods suspected of provoking a reaction must be completely eliminated. The resolution of symptoms suggests that the food may be responsible, while the continuation of symptoms indicates that some other cause should be explored. The elimination diet alone is insufficient to diagnose food allergy, but both positive and negative results

contribute to focus the diagnostic investigation.

B. Laboratory tests

Neither SPT nor *in vitro* specific IgE testing alone is sufficient for the diagnosis of food allergy. An individual may be sensitized, thus producing specific IgE, without clinical symptoms. Recent studies in patients with eczema suggest that up to 93% of patients with food-specific IgE were able to reintroduce the food after tolerating an oral food challenge. The patient history should guide the choice of foods to evaluate with these tests, and the interpretation should be made with that clinical history in mind.

C. Allergy skin test

Epicutaneous SPT are highly reproducible when performed by trained individuals and often used to screen for IgE-mediated allergies. Because SPT assess for the presence of IgE bound to cutaneous mast cells, it will not aid in the diagnosis of non–IgE-mediated diseases, for example, celiac disease or lactase deficiency. Additionally, the lack of standardization of commercial food extracts as well as possible protein degradation during the extraction process may limit the usefulness of SPT to diagnose food allergy in fresh foods. In some patients, it may be necessary to employ a prick–prick SPT whereby fresh food is used in the testing. The fresh food is first pricked, and then the patient's skin is pricked to introduce the potential allergen into the skin. A wheal diameter 3 mm greater than the negative control denotes a positive SPT. A positive SPT indicates only the possibility of reaction to the food (overall positive predictive value <50%), while a negative SPT confirms the absence of specific IgE (overall negative predictive value >95%).

Intradermal skin testing has increased sensitivity over SPT but carries a higher risk of provoking an anaphylactic reaction and is not recommended for evaluating food allergy. Intradermal testing is less specific than a double-blind, placebo-controlled food challenge (DBPCFC). Due to these limitations, intradermal testing does not have a role in the diagnosis of food allergy. At this time, there are insufficient data to support the use of patch testing in the diagnosis or management of IgE-mediated adverse food reactions. Patch testing with single-ingredient foods suspected of triggering EoE may provide targeted elimination diet but should be validated with reintro-duction of the suspected food after an elimination period of 5 to 7 weeks. Return of symptoms within 5 to 7 days after including the suspected food supports continued elimination of the food from the diet.

D. *In vitro* testing

While total serum IgE should not be used in the diagnosis of food allergy, food-specific IgE may support the possibility of food allergy. As with SPT, a negative specific IgE is useful to rule out food allergy, although presence of specific IgE does not establish the diagnosis. The current standard of detection of specific IgE uses a capsulated hydrophilic carrier polymer-fluoroenzyme immunoassay (CAP-FEIA), and several systems are available. Studies have indicated that while each system is adequate at detecting specific IgE, the values reported are not interchangeable between systems. Detection of food-specific IgE does not indicate allergy, but several studies have found correlation between the specific IgE level and likelihood of reaction after ingestion. Table 16-5 lists specific IgE levels using the ImmunoCAP system (Phadia, Sweden) with the reported positive predictive value of reaction f ollowing ingestion.

Table 16-5 Specific IgE

Allergen	Decision Point	Positive Predictive Value Reaction Follows Ingestion
Milk		
Infants <24 mo	5 kU/L	95%
Children >24 mo	15 kU/L	95%
Egg		
Infants <24 mo	2 kU/L	95%
Children >24 mo	7 kU/L	98%
Peanut	14 kU/L	100%
Tree nuts	~15 kU/L	~95%
Soy	30 kU/L	73%
Wheat	26 kU/L	74%

IX. ORAL FOOD CHALLENGE

Recently published guidelines recommend oral food challenges for the diagnosis of food allergy. The DBPCFC remains the gold standard because it signifi-cantly reduces bias by both patient/parent and the physician during the procedure. Because of the difficulty performing a DBPCFC in the clinic setting, an open challenge or single-blind challenge may also be diagnostic provided the following criteria are met: If no symptoms are elicited, then the challenge is negative, and food allergy may be ruled out. Should objective symptoms develop, which are consistent with the patient's history, and supportive laboratory tests are present, the food challenge would support the diagnosis of food allergy. Example protocols for an open oral food challenge using highly heated egg and a double-blind oral food challenge with placebo using peanut may be found in the Appendix to this chapter.

X. UNPROVEN DIAGNOSTIC AND THERAPEUTIC TECHNIQUES

Because of the lack of complete understanding about the basic immunopathologic mechanisms and the prevalence of individuals believing they have an adverse food reaction, numerous medical techniques have been developed for the diagnosis and treatment of these problems. Disproven or unproven techniques include cytotoxicity testing, provocative and neutralization treatment, autogenous urine immunization, IgG subclass diagnosis of food allergy, and food immune complexes. These methods should not be used in the evaluation of food allergy. Tests for IgG or IgG4 to a specific food or specific food immune complexes have been proposed for use in the diagnosis of food allergic reactions, but there is little evidence to support their use. Development of food-specific IgG and IgG4 is a normal immune response to food ingestion. Similarly, immune complex formation is a normal event in the course of an immune response and allows antigen elimination. Masking and addiction, rotary diets, and fasting are all various techniques of dietary manipulation that have shown to have no role in the diagnosis or treatment of food allergic diseases.

XI. TREATMENT

There are currently no FDA-approved treatments for food allergy. Current recommendations are for strict avoidance of the food allergen in the diet as well as prompt treatment when symptoms develop after inadvertent ingestion. Establishing the diagnosis of food allergy is critical to avoid unnecessary dietary restrictions that may affect growth and development. No studies are available to show that avoidance will affect the natural course of food allergy toward either

tolerance or persistence. Patients and families must be educated on the importance of reading ingredient labels and must ask about ingredients in meals consumed in restaurants. Often, nutritional counseling by a registered dietitian is necessary to maintain adequate nutritional intake. Studies have demonstrated that accidental exposures occur frequently and patients must be prepared to intervene before the arrival of medical assistance.

Even with careful shopping and other precautions, accidental exposures occur. Some studies site an accidental exposure every 18 to 24 months per patient. A written food allergy action plan should be given to each patient. An example may be found at http://www.foodallergy.org/files/FAAP.pdf. This written plan provides instructions to patients as well as caregivers in the case of accidental exposure. Quick access to injectable epinephrine should be emphasized, and the patient/family should be familiar with the use of their individual device.

XII. FUTURE THERAPY

Current investigational studies may soon offer active therapy for food allergy. Several studies have demonstrated that food allergen may be safely delivered either sublingually or orally in order to induce desensitization. Subjects in these studies do demonstrate adverse effects (i.e., hives, oral pruritus, abdominal pain, and respiratory distress) during the administration of these experimental doses. At this time, the appropriate clinical dose and length of therapy necessary to induce tolerance have yet to be determined.

SUMMARY

Food protein causes both IgE- and non–IgE-mediated disease. Life-threatening reactions are likely to be caused by IgE directed against specific proteins. Non–IgE-mediated food reactions lead to chronic conditions that may adversely affect normal growth and development. Avoidance of triggering foods is often difficult, and accidental exposures lead to exacerbation of disease and potentially life-threatening anaphylaxis. Although most food reactions are not fatal, early recognition of food allergy symptoms with immediate access to injectable epinephrine may prevent adverse outcomes. Education of patients and their family continues to hold a vital role in the treatment of both IgE- and non–IgE-mediated food reactions. Appendix V lists several educational resources.

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APPENDIX: ORAL FOOD CHALLENGE PROTOCOLS

Open Challenge Using Baked Egg

Setting: Oral food challenges should be carried out under the supervision of a physician in an appropriately stocked clinic and staffed with medical personnel trained to recognize and treat anaphylaxis.

Purpose: To identify those egg-sensitive patients who will tolerate heated egg products

Patient selection (this is only a suggestion, final decision to be made by caregiver): For heated egg challenges, patients could have an ovomucoid-specific IgE ≤2 kU/L and an epicutaneous skin prick test to egg <8 mm.

Preparation: Patients must be off nonsedating antihistamines for 7 days before the challenge; diphenhydramine may be continued for up to 4 days before the visit. The challenge food must have

been excluded from the diet for at least 2 weeks. All other medications may be continued (inquire about other drugs with significant antihistaminic activity such as imipramine). If patients are unable to fast prior to the challenge, a light meal that is low in fat is recommended at least 2 hours before the challenge.

Food source: Food for the challenge will be prepared by the family before coming to the challenge. A recipe will be provided prior to the visit. Please see below for specific recipe.

Challenge material will be one serving size of a heated egg product containing approximately 5 g of egg protein (3/4 of one egg). Challenge material amount is equivalent to the typical quantities found in the home-baked and commercial food products. Intervals are minimum waiting times between increments. If intake is slow, attempt to complete entire serving in no more than 2 hours.

Timetable

Time (min)	Amount (Fraction of Serving)	Cumulative Amount (Fraction of Serving)
0	1/32	1/32
15	1/16	3/32
30	1/8	7/32
45	1/4	15/32
60	1/2	Full serving

Reactions: Common reactions are facial/truncal erythema and macular rash with itching. Abdominal pain, nausea, vomiting, and itching of the eyes and nose with sneezing are frequent as well. Unusually, patients might develop wheezing, throat constriction, or hypotension. No further incremental doses are administered if challenge is judged positive. For all challenges, emergency medications should be available at the bedside. These include:

1. Epinephrine, which should be preloaded in a syringe (0.01 mL/kg of 1:1000)
2. Oral diphenhydramine (1 mg/kg)
3. Oral prednisolone (1 mg/kg)

Patient may be discharged home if no reaction occurs 1 hour after completing the challenge. If they do have a reaction, they may be discharged home once the symptoms have resolved and no sooner than 1 hour.

Heated Egg Cake

Sponge Cake (one serving is approximately 5 g of egg protein)
5 eggs, separated
1 cup white sugar
4 tablespoons cold water
1 cup sifted cake flour
1 teaspoon baking powder

1. Preheat oven to 350 degrees. Grease a tube pan.
2. Beat egg yolks and sugar together until very light. Add water. Sift together flour and baking powder. Add to batter. Beat egg whites until stiff. Fold into batter. Pour batter into prepared pan.
3. Bake for 30 to 35 minutes until brown and pulls away from the edge of the pan.
4. Cut into eight servings.

Double-Blind, Placebo-Controlled Food Challenge Using Peanut

Setting: Oral food challenges should be carried out under the supervision of a physician in an appropriately stocked clinic and staffed with medical personnel trained to recognize and treat anaphylaxis.

Purpose: To identify those peanut-sensitive patients who tolerate peanut in the diet

Patient selection (this is only a suggestion, final decision to be made by caregiver): For peanut oral challenges, patients could have a peanut-specific IgE ≤2 kU/L and an epicutaneous skin prick test to peanut <8mm. The patient should have experienced no accidental ingestion of peanut with adverse reaction within the past 6 months.

Preparation: Patients must be off nonsedating antihistamines for 7 days before the challenge; diphenhydramine may be continued for up to 4 days before the visit. All other medications may be continued (inquire about other drugs with significant antihistaminic activity such as imipramine). If patients are unable to fast prior to the challenge, a light meal that is low in fat is recommended at least 2 hours before the challenge.

Food source: A single-serving 21-g container of commercial peanut butter, approximately 2 teaspoon (tsp), may be used. The peanut butter should be mixed in sufficient quantity of a vehicle food, for example, chocolate or banana pudding, which will mask the taste and smell of the peanut butter.

Timetable

Time (min)	Amount (Fraction of Serving) Mixed into Vehicle Food	Cumulative Amount (Fraction of Serving)
0	1/32 tsp (size of grain of rice)	1/32 tsp
10	1/16 tsp (size of kernel of corn)	3/32 tsp
20	1/8 tsp	7/32 tsp
30	1/4 tsp	15/32 tsp
40	1/2 tsp	31/32 tsp
50	1 tsp	~2 tsp

Intervals are minimum waiting times between increments. If intake is slow, attempt to complete entire serving in no more than 2 hours.

Reactions: Common reactions are facial/truncal erythema and macular rash with itching. Abdominal pain, nausea, vomiting, and itching of the eyes and nose with sneezing are frequent as well. Unusually, patients might develop wheezing, throat constriction, or hypotension. No further incremental doses are administered if challenge is judged positive. For all challenges, emergency medications should be available at the bedside. These include:

1. Epinephrine, which should be preloaded in a syringe (0.01 mL/kg of 1:1,000)
2. Oral diphenhydramine (1 mg/kg)
3. Oral prednisolone (1 mg/kg)

Patient may be discharged home if no reaction occurs 1 hour after completing the challenge. If they do have a reaction, they may be discharged home once the symptoms have resolved and no sooner than 1 hour.

17

Eosinophilic Gastrointestinal Diseases

Terri F. Brown-Whitehorn, Kernika Gupta, Ritu Verma, and Jonathan M. Spergel

DEFINITIONS OF EOSINOPHILIC GASTROINTESTINAL DISEASES

Eosinophilic Gastrointestinal Diseases (EGIDs) are allergic and/or inflammatory conditions defined by the presence of an abnormal level of eosinophils in the gastrointestinal (GI) tract, in absence of idiopathic hypereosinophilic syndrome, parasitic infection, drug reaction, and inflammatory bowel disease (IBD) or other causes of eosinophilia. It is important to remember that eosinophils can exist normally in the GI tract. The number of eosinophils varies in different parts of the GI tract, ranging from zero in the esophagus to 20 to 40 in the stomach and colon (Fig. 17-1). EGIDs are divided based on the location of abnormal eosinophils, esophagus (eosinophilic esophagitis [EoE]), colon (eosinophilic colitis [EC]), or entire GI tract (eosinophilic gastroenteritis [EG]). For all classifications of EGIDs, symptoms can include failure to thrive, dysphagia, food impaction, abdominal pain, and reflux that are nonrespon-sive to proton pump inhibitors (PPIs), while lower abdominal symptoms (diarrhea, bloating) being more common in EG and EC. These clinical symptoms alone are nonspecific to EGIDs, and symptoms can occur continuously or variably over time in individuals with EGIDs.

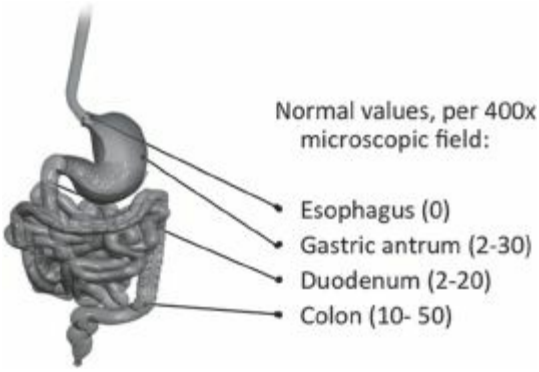

Figure 17-1. Normal amount of eosinophils located in the gastrointestinal tract.

I. TYPES OF EGIDS

A. Eosinophilic Esophagitis (EoE) is characterized by the presence of 15 or more eosinophils per high power field and inflammation in the esophagus. However, eosinophils can occur in the esophagus from other etiologies including gastroesophageal reflux disease (GERD), allergic rhinitis, fungal infection, and IBD. Due to this confusion, two consensus meetings have occurred with development of agreed-upon definition with most recently published in 2011.

Eosinophilic esophagitis represents a chronic, immune/antigen mediated, esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation… Eosinophilic esophagitis (EoE) is a chronic clinico-pathological disorder of the esophagus, characterized by a spectrum of symptoms referable to esophageal dysfunction that occur in association with esophageal mucosal biopsy specimens

containing ≥15 intraepithelial eosinophils/high power field (HPF) in one or more biopsy specimens. The disease is isolated to the esophagus and other causes of esophageal eosinophilia must be excluded. Typically, the disease remits with treatments including dietary exclusions and/or topical corticosteroids.

EoE can affect both children and adults, with some variation in symptom presentation (detailed below). There are several consistent features: highly atopic with >70% of patients having at least one feature of atopy (asthma, allergic rhinitis, IgE-mediated food allergies, or atopic dermatitis) and a strong male predominance 3:1.

B. Eosinophilic Gastroenteritis (EG) is characterized by the presence of various GI symptoms and the presence of 30 or more eosinophils present in the GI tract, most commonly in the gastric antrum or small bowel. EG affects both children and adults but tends to dominate more in males. Clinical symptoms can include abdominal pain, diarrhea, weight loss, and vomiting, which are all nonspecific to EG. The symptoms and clinical presentation are typically more severe than EoE. Other symptoms that can be a sign of severe disease include GI bleeds, anemia, and hypoalbuminemia, also nonspecific findings. These symptoms can mimic numerous other conditions such as IBD, chronic granulomatous disease (CGD), *Helicobacter pylori* infection, parasitic infection, idiopathic hypereosinophilic syndrome, or even hypertrophic pyloric stenosis in infants. Potential laboratory tests to consider in a workup of EG include serum IgE level, stool studies, allergy testing, IBD panel, CBC/differential, complete metabolic panel, and radio-logic studies, as well as a mandatory endoscopy and colonoscopy.

C. Eosinophilic Colitis (EC) is a rare manifestation of EGIDs that is characterized by the presence of abnormal level of eosinophils in the colon, in absence of any other condition related to hypereosinophilia such as inflammatory bowel disease, parasitic infections, drug reactions, or autoimmune connective disorders. Additionally, the presence of eosinophils in the colon may be due to allogeneic bone marrow transplantation, Tolosa-Hunt syndrome, and idiopathic hypereosinophilia syndrome, all of which rarely can manifest by EC. The etiology behind EC is most obscure of all the EGIDs. In some cases, EC might be precursor of IBD as eosinophils can occur in IBD in isolation. Diagnosis is dependent on the presence of an abnormal level of eosinophils in the colon, which is dependent on what area biopsies are taken. Normal levels of eosinophils for the rectum are <10 eosinophils per high power field but can be >30 eosinophils per high power field in the cecum (Fig. 17-1). Therefore, biopsy location correlating eosinophil levels are highly important in the diagnostic procedure for EC. Many children with EC may have complete resolution of symptoms over time without intervention, whereas others may have resolution based on removal of atopic agents defined as the possible triggers for EC. In adults, EC may resolve without intervention or after removal of atopic agents, but there is a chance for relapse despite removal of atopic agents.

II. PREVALENCE AND INCIDENCE

The actual incidence and prevalence of EGIDs are hard to estimate as ICD-9 diagnostic codes have only been recently established in 2008: Eosinophilic Esophagitis—530.13, Eosinophilic Gastritis—535.7, Eosinophilic Gastroen-teritis—558.41, and Eosinophilic Colitis—558.42. However, estimates for EoE have been done in two ways: (1) random sampling/biopsy of local population and (2) examining the number of patients seen in local population. The major issue

with the random sampling of a population is that other causes of esophageal eosinophilia have not been ruled out. In addition, the prevalence rates are related to the number of eosinophils used as the diagnostic criteria with rates as high as 1,100/100,000 when it was based on >10 eosinophils/ HPF. Examination of local populations has found an estimated prevalence that is much lower, around 7 to 70/100,000, in the United States and Switzerland. This suggests that many cases of EoE are possibly being missed and we are just seeing the tip of the iceberg. To get a national estimate, we recently completed an Internet survey of all gastroenterologists and allergists in the United States and asked them to estimate the number of new patients that they see in one year. Based on their numbers and population in each state, we calculated an overall prevalence of EoE in the United States at 52/100,000 population, similar to the local estimates.

The other interesting observation seen in several centers is that there has been a large and steady growth in almost exponential fashion in the number of cases of EoE diagnosis in the last 10 to 15 years. However, recent studies have suggested that a large portion of this increase might be due to increased number of procedures and recognition of the disease.

The epidemiology of EG and EC has not been well studied, and estimates are unclear because most studies are small. Our same Internet survey of US gastroenterologists found an estimate for combination of EG and EC at 28/100,000 population, indicating these are rare diseases.

III. PATHOGENESIS OF EGIDS

Eosinophilic esophagitis has been proposed to be atopic dermatitis of the esophagus based on murine and human studies. Like several other diseases, individuals likely have a genetic susceptibility and an allergen trigger leading to recruitment of inflammatory cells and disease.

A. Genetic susceptibility

EoE is similar to most atopic diseases being multifactorial. However, EoE has a stronger genetic component with high sibling risk ratio of 80 compared to asthma at 2. Candidate gene studies have identified eotaxin-3 and thymic stromal lymphopoietin (TSLP) as being important. There have been no genetic studies done on EG or EC.

B. Allergen trigger

Both foods and aeroallergens can induce EoE. In human models, pollen exposure in patients with allergic rhinitis induces esophageal and duodenal eosinophilia but typically not to levels seen in EoE. In almost all patients (adult and pediatrics), foods have been shown to be a trigger for EoE, and removal of the food resolves eosinophilia, and reintroduction causes EoE.

C. Inflammatory cells

EoE has other inflammatory cells, such as TH2 cells and mast cells, which contribute to the symptoms and progression of the disease. Esophageal biopsies show marked TH2 inflammatory responses. IL-13, IL-4, TGF-b1, and STAT 6 are all thought to be important factors in disease pathogenesis. Periostin is induced by IL-13 and regulates eosinophil recruitment and adhesion, promoting a cycle of increased disease. Children with untreated eosinophilic esophagitis have basement membrane thickening and increased vascular activation, similar to changes seen in airway remodeling and asthma. Fibrosis and dysmotility lead to esophageal dysfunction and dysphagia in patients.

D. Atopic nature of EGID

Patients with EGID, especially EoE, are much more likely to be atopic than the general

population. In the United States, 8% of adults and 10% of children have asthma, 10% to 30% of adults and 40% of children have allergic rhinitis, 3% of adults and 10% to 20% of children have atopic dermatitis, and 3% to 4% of adults and 6% of children have IgE-mediated food allergy. In comparison, 80% of EGID patients in a world-wide registry were atopic (38% had asthma, 64% had allergic rhinitis, 26% had atopic dermatitis, and 23% had IgE-mediated food allergy). Two-thirds of our pediatric patients at The Children's Hospital of Philadelphia had atopy in our recent 14-year review. Similar high rates were seen in adults with almost 2× the rate of atopy than the general population (asthma—26%, allergic rhinitis—78%, and atopic dermatitis—3%) (Table 17-1).

Table 17-1 Studies Showing the Frequency of Atopic Disease (%) in Normal Population and EoE Patients

Location/yr	# EoE pts	Age (yr)	Asthma	AR	AD	Food Allergy (Anaphylaxis)
US kids			10%	40%	10%–20%	6%
US adults			8%	10%–30%	3%	3%–4%
World wide web 2002	39	8 ± 12	38%	64%	26%	23%
Australia, 2006	26	17 to 65	50%	46%	1%	27%
Australia, 2007	45	3 m to 16 y	66%	93%	55%	24%
Cincinnati, OH; 2007	89	6.2 ± 4.8	39%	30%	19%	9%
Philadelphia, PA UPENN 2008	23	18–57	26%	78%	4%	
Philadelphia, PA CHOP 2009	620	9.1 ± 3.1	37%	39%	13%	5.7%
Jacksonville, FL; 2009	41	52 (mean)	15%	17%		15%
Vancouver, Canada; 2010	54 adults		43%	70%		
San Diego, CA; 2010	32	1 to 16	34%	50%	22%	

Abbreviations: AR, allergic rhinitis; AD, atopic dermatitis; FA, food allergy.

1. **Food allergens:** The role of food allergies in EoE has been clearly defined and has fulfilled Koch's postulate. Many studies have shown that removal of foods with an elemental diet led to resolution of all symptoms and normalization of endoscopy and biopsy. Either empiric or allergen testing–derived elimination of individual foods also leads to resolution of symptoms and endoscopic and histologic features in 70% to 80% of pediatric patients. The reintroduction of the positive foods leads to symptoms and esophageal eosinophilia returning, fulfilling Koch's postulate that food can cause EoE.
2. **Aeroallergens:** Aeroallergens may play a role in EoE and EG based on several key facts. Patients with EoE are sensitized to a variety of aeroallergens. Diagnosis of new EoE cases increases during pollen seasons. Pollen can cause esophageal eosinophilia. It has been shown that pateints with allergic rhinitis have esophageal eosinophilia when they have endoscopies and biopsies during grass pollen season and that the biopsy worsened during the pollen season and normalized outside of the pollen season while the diet and medications remained unchanged. Although pollen plays a role in patients with EoE, most often it is not the only trigger. For EG, allergic patients were also shown to have an increase in eosinophils and IgE-bearing cells in the duodenum during the tree pollen season as compared with off-season.

IV. SYMPTOMS OF EGID

The symptoms of EGID vary by disease and age of the patient (Tables 17-2 and 17-3). Infants and toddlers with EoE can present with gastroesophageal reflux, vomiting, feeding difficulties, irritability, and, at times, failure to thrive (Table 17-3). For EoE, school-age children present with reflux symptoms, vomiting, and abdominal pain. Adolescents and adults with EoE most

commonly present with dysphagia, although chest pain, upper abdominal pain, "heartburn," and food impactions occur. Over time, patients may compensate by taking smaller bites, drinking a lot of fluids, avoiding certain foods, avoiding certain textures, and/or eating slowly. No one symptom is specific for EoE; however, some symptoms are highly suggestive such as food impaction, which has been shown to occur in over 50% of adult patients. Symptoms and peripheral markers are nonspecific, and diagnosis needs to be confirmed by endoscopy and biopsy of the GI tract. An endoscopy on proton pump inhibitor and potential nasal steroid is necessary for diagnosis as GERD and allergic rhinitis can cause eosinophils in the esophagus. In terms of follow-up of EoE patients, repeat endoscopy and biopsies are needed, as symptom scores did not correlate with degree of inflammation seen on biopsy.

Table 17-2 Symptoms, Testing, and Pathology for EGIDs

EGIDs	Symptoms	Potential Testing	Histopathology
EoE	Dysphagia, food impaction, abdominal pain, reflux, failure to thrive, nausea, vomiting	Laboratory tests (IgE, CBC, CRP, ESR), stool studies (ova and parasites, FCP), barium studies, upper endoscopy	15 or more eosinophils per high power field in the esophagus
EG	Abdominal pain, diarrhea, weight loss, dysphagia, nausea, vomiting	Laboratory tests (IgE, CBC, CRP, ESR), stool studies (ova and parasites, FCP), barium studies, upper endoscopy, and possible colonoscopy	20 or more eosinophils per high power field in stomach
EC	Abdominal pain, diarrhea, failure to thrive, nausea, vomiting	Laboratory tests (IgE, CBC, CRP, ESR), stool studies (ova and parasites, FCP), barium studies, upper endoscopy, and colonoscopy	Abnormal amounts of eosinophils is dependent on region of colonic biopsy, can range from 10–30+ eosinophils per high power field

Table 17-3 Age-Associated Symptoms for Eosinophilic Esophagitis

Age	Symptoms
Infants and young children	Vomiting Gastroesophageal reflux Feeding difficulties Irritability
School age	Gastroesophageal reflux Abdominal pain
Adolescents	Dysphagia Food impaction Abdominal pain Gastroesophageal reflux
Adults	Dysphagia Food impaction Chest pain Upper abdominal pain Gastroesophageal reflux

At times, patients and their families will describe "classic symptoms," or on examination, there will be growth concerns. However, because many of the symptoms are reflux-like, abdominal pain or vague, diagnosis is often delayed. It is important to ask the correct questions as many patients have compensated for disease process. Do you cut your food into small bites, drink a lot of water, or eat slowly? If the answer is yes, further evaluation is necessary. In both adults and

children, there is often a 3- to 4-year lag time between symptoms and diagnosis.

EG and EC are less common diagnoses than EoE. These patients typically have lower GI symptoms, diarrhea, bloody stools, mucous stools, and abdominal pain (Table 17-2). Patients with EG may also have concomitant reflux symptoms, dysmotility, and stool changes. Children may present quite ill appearing with pallor and fatigue. Diagnosis is made with endoscopy and colo-noscopy. Exclusion of other diagnoses is important, and potential laboratory evaluation includes metabolic panel, CBC with differential, IgE levels, infectious workup, and stool studies, and if hypereosinophilia, hematology evaluation, tryptase level, and evaluation for FIP1/L1 PDGFRA fusion protein (for mastocytosis with eosinophilia) should be considered.

V. NATURAL HISTORY

Infants and toddlers who are diagnosed with eosinophilic esophagitis often have gastroesophageal reflux symptoms, most often related to food allergies. As children grow older, many will present more with vomiting and abdominal pain. Adolescents and adults often present with dysphagia and at times food impaction (Table 17-3). These constellations of symptoms suggest a natural history of disease. Confirming this potential scenario, we found in a retrospective review of 24 patients that were lost to follow-up and returned 6 years later that dysphagia was very common (compared to abdominal pain and GERD symptoms at presentation). This suggests a natural history of chronic inflammation over time, leading to esophageal dysfunction, increasing fibrosis, and eventually narrowing of esophagus with strictures and food impactions (Fig. 17-2). Consistent with this theory, small-caliber esophagus and spontaneous perforation may occur in adults and adolescents. EoE is a chronic condition as <5% of children outgrow EoE and adults typically showed no resolution. However, the sensitization may change with time as aeroallergens seem to be more important than foods in adults.

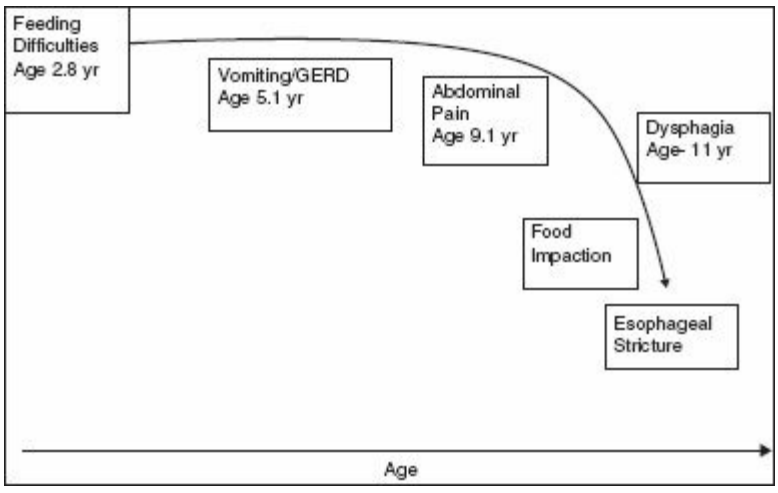

Figure 17-2. Proposed natural history of eosinophilic esophagitis. Natural history of EoE with changing of symptoms and increasing esophageal dysfunction. (Reprinted from Spergel JM, Brown-Whitehorn TF, Beausoleil JL, et al. 14 years of eosinophilic esophagitis: clinical features and prognosis. *J Pediatr Gastroenterol Nutr* 2009;48:30–36, with permission.)

VI. ENDOSCOPIC AND HISTOLOGIC FINDINGS

A. Endoscopy: Patients must undergo an esophagogastroduodenoscopy as the current gold standard for diagnosing an EGID. Endoscopic findings among all subsets of EGIDs may demonstrate inflammation, typically patchy, in a particular area of the GI tract, friability, and

erythema. When evaluating for EoE, typical features that can be reported during endoscopic evaluation includes concentric rings also called "feline esophagus," esophageal strictures, linear furrowing, and sometimes white lesions, which are an indication of abscesses (Fig. 17-3).

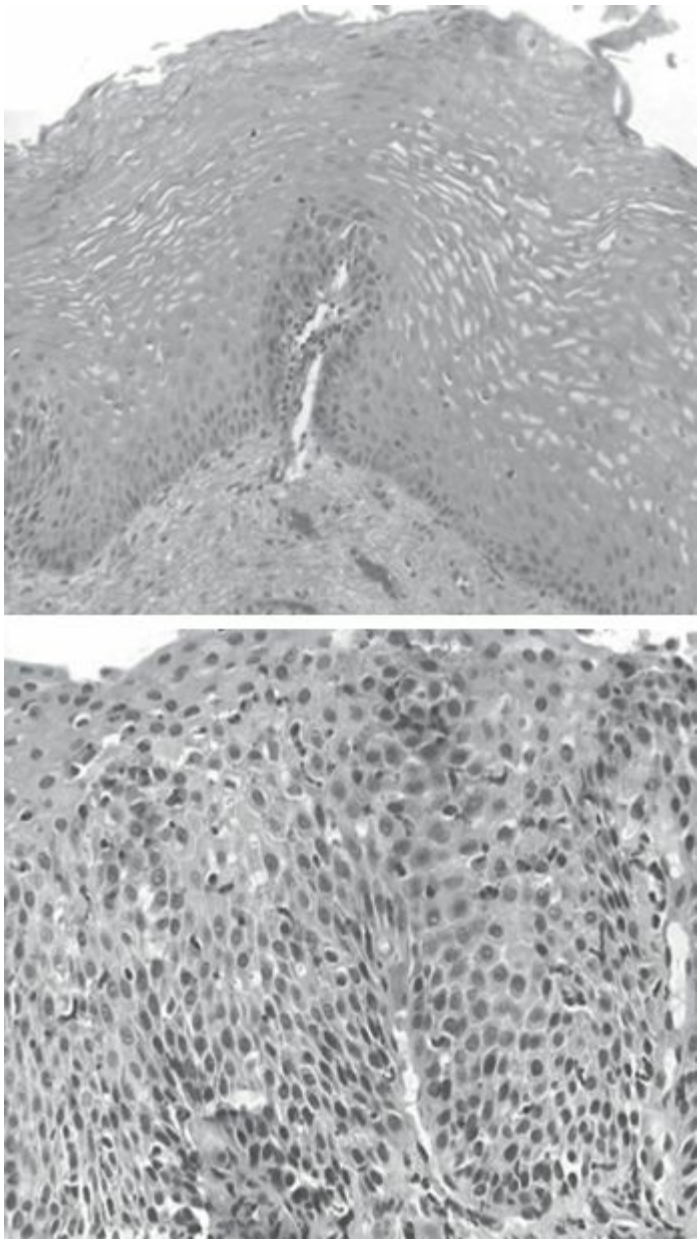

Figure 17-3. Histological findings noted in eosinophilic esophagitis. **A:** Normal esophagus. Note no eosinophils, hyperplasia. **B:** Eosinophilic esophagitis. Note increased number of eosinophils, basal hyperplasia, and thickening of the surface epithelium.

In rare cases, there may also be the presence of perforation. Endoscopic evaluation for EoE is the most concrete among all EGIDs based on its unique and typical presentation. However, endoscopic evaluation for EG and EC may depict patchy inflammation, erythema, friability, and possibly hyperplasia, but these are common features of a variety of other conditions. Individuals being evaluated for EG or EC must also undergo a colonos-copy to evaluate part of the small bowel and the colon in addition to an esophagogastroduodenoscopy.

B. Histology: Histology is essential to the correct diagnosis of EGIDs in the setting of nonspecific clinical symptoms and absence of other conditions, as mentioned previously. Histological findings should demonstrate eosinophils in the squamous epithelium, and the level of eosinophils varies by section of the GI tract, stressing the importance of correlation of eosinophil levels to area of biopsies. In cases of EoE, the presence of 15 or more eosinophils per high power field

in the mid-esophageal or upper esophageal areas is strongly suggestive for a diagnosis of EoE (Fig. 17-1). Other histologic features that may be present include basal-zone hyperplasia, an increase in papillary size, and microabscesses of eosinophils. In EG, histological findings should also demonstrate eosinophils in the squamous epithelium of the GI tract, mostly concentrated in the gastric antrum and small bowel. Recent studies show significant involvement of the mucosal layer in EG. Biopsies of the GI tract should demonstrate the presence of 30 or more eosinophils per high power field and can have a patchy presentation indicating the importance of multiple biopsies throughout the GI tract. EC is the rarest subset of EGIDs, and many of the endoscopic and histological findings can be indicative of numerous other conditions, causing this disease to be one of exclusionary diagnosis. In the rectum, a normal level of eosinophils can be 10 or less per high power field, whereas in the cecum, a normal level can be >30 eosinophils per high power field. Eosinophilic infiltrate can be found in the lamina propria throughout the colon but typically manifests as patchy inflammation. Diagnosis of EGIDs based on histological findings are dependent on the presence of abnormal levels of eosinophilic infiltrate in the lamina propria based on area of the GI tract and no other evidence for other conditions such as GERD, IBD, or parasitic infections.

Endoscopic evaluation for EGIDs is the current gold standard, but radio-logic findings are prime contributors to assessing the GI tract and evaluating parts of the small bowel that cannot be reached through esophagogastroduode-noscopy or colonoscopy. When evaluating individuals for EoE, barium studies can easily and safely assess the presence or degree of esophageal strictures, as well as long-segment narrowing, and possibly the presence of esophageal rings (see Fig. 17-4). Barium studies in evaluation for EG or EC can also reveal mucosal thickening, luminal narrowing, or ulcerations. Specifically indicative of EG based on radiological findings may be the presence of *areae gastricae*, which is a specific mucosal pattern. Barium studies can be extremely useful for long-term follow-up to assess progression or resolution of the disease (Fig. 17-5).

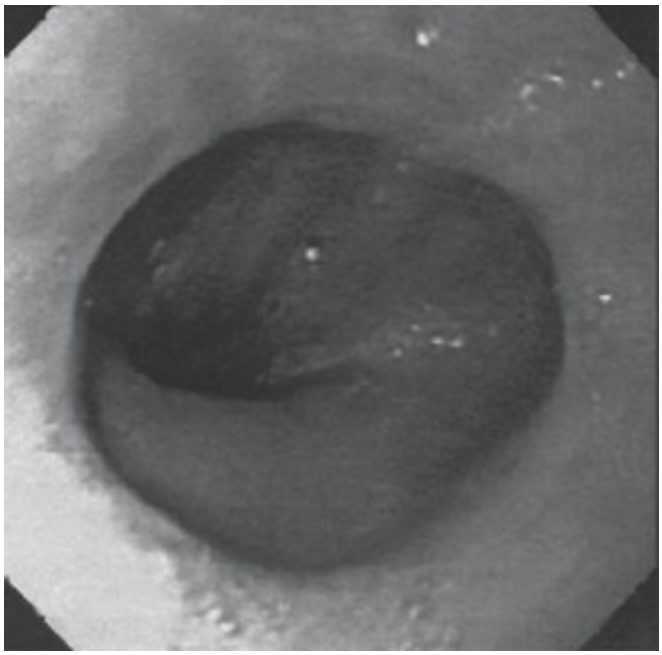

Figure 17-4. Endoscopy findings. Esophageal rings and feline esophagus noted on upper endoscopy in eosinophilic esophagitis.

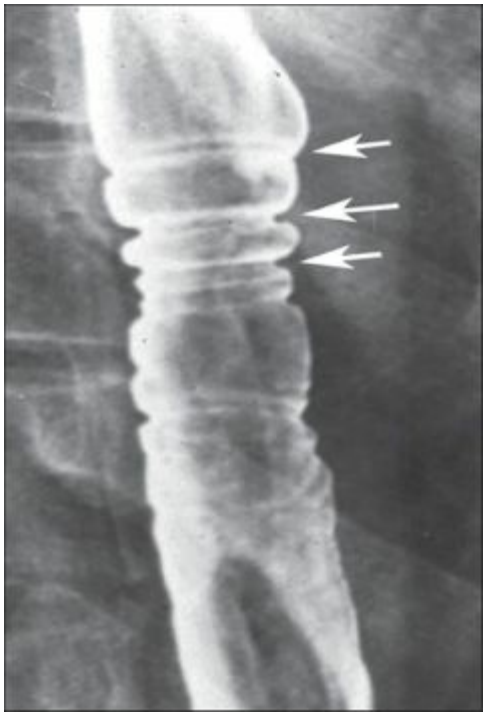

Figure 17-5. Barium swallow of eosinophilic esophagitis. Narrowing of the esophagus and strictures noted on barium swallow. Arrows note esophageal rings.

VII. POTENTIAL LABORATORY TESTS

Laboratory evaluation for individuals who present with clinical GI symptoms tend to be standard across the spectrum including a complete blood count (CBC), comprehensive metabolic panel, and inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). CRP and ESR serum levels are indicative of inflammation present in any area of the body, not specific to the GI tract, but are excellent indicators of an abnormal process currently taking place. Individuals with EGIDs tend to have low hemoglobin, indicating iron deficiency anemia, as well as a low albumin, which may be indicative of malabsorption and a protein-losing enteropathy. These are nonspecific abnormalities and can be evident in a variety of other conditions affecting the GI tract. No specific markers correlate with EGID biopsy findings despite extensive searches including cytokines, eotaxin-3, eosinophilic markers (major basic protein, neurotoxin, and cationic protein), and stool markers.

Stool studies are an essential part of a GI workup as they provide a window into what ova, parasites, bacteria, or other organisms may be residing in the GI tract, as well as provide an excellent indication of intestinal inflammation. Stool tests that look at ova and parasites and test for a variety of other infections such as Salmonella, Shigella, and Clostridium difficile are essential to perform. These infections or other parasitic infections can mimic the GI symptoms individuals may have and possibly explain the etiology for the intestinal inflammation. Stool tests for the presence of white blood cells and eosinophilia may be helpful to capture an understanding of what is present in the GI tract prior to treatment. Fecal calprotectin (FCP) is a measure of inflammation in the intestines and has been useful for diagnosing IBD. While testing for ova and parasites can be helpful to explain other etiologies and obtaining a FCP result is helpful to characterize the degree of inflammation in the intestines, there is no absolute stool test that is helpful in diagnosing EGIDs.

VIII. TREATMENT FOR EGID

A. Treament for EoE

Management of EoE involves elimination/control of eosinophils with either medications or diet. Medical treatment involves treating the symptoms but not the cause of the disease. It is important to note that there are no current approved medications for the treatment of EoE, EG, or EC. However, the use of "topical" corticosteroids has been shown to be successful in EoE. Dietary therapy is based on removing the causative agent. However, dietary therapy can be difficult if removal of multiple foods leads to potential low quality of life and need for supplementation with elemental formula to prevent malnutrition. Therefore, balancing between medical therapy and dietary therapy is dependent on the individual, family, and physician.

1. Dietary approach

One approach is treating the cause of the disease, eliminating the suspected food. An elemental diet has been successful in both pediatric and adult patients, with success rates approaching high 90%. However, due to poor palatability of these formulas, it is difficult for patients to remain on these formulas. A more directed approach of eliminating the particular food antigen is possible. There are two possible ways to remove the food antigen: (1) removing the most common food allergens or (2) removing the allergens based on allergy testing. Using a "six-food" elimination diet (no milk, soy, egg, wheat, seafood (fish and shellfish), and peanut (peanuts and tree nuts)), there is a 50% to 75% reduction of esophageal eosinophilia in children and adults. This is even better with an elemental diet (personal communication, Gonsalves).

a. Allergy testing–directed diet: The alternative dietary approach is to remove foods based on allergy testing. There are three standard methods for food testing: prick skin testing, *in vitro* specific IgE, and atopy patch tests. Diet based on positive specific IgE has a response rate of near zero percent when foods are eliminated based purely on *in vitro* specific IgE. However, it has been reported that serum assays depicted more positive testing to milk compared to skin prick test (SPT) and atopy patch test (APT). Eighty percent of the patients had positivity to either food and/or aeroallergens.

The use of prick skin tests only had a slightly better success rate of about 50%. This strongly suggests that the food allergy in EoE is not strictly IgE mediated consistent with the results with omalizumab (anti-IgE), which showed no improvement in symptoms or histology. Atopy patch testing is designed to look for non–IgE-mediated food reactions, presumably T cell mediated. We have found the combination of both prick skin testing and atopy patch testing looking for both IgE and non–IgE-mediated disease has been highly successful in the treatment of EoE. We remove foods that are positive on skin or patch testing. The most common foods by skin prick testing were milk, eggs, peas, peanuts, wheat, beef, rye, and potatoes. The most common foods by patch testing were milk, egg, soy, wheat, rye, and corn. If a child is skin prick test positive to a food, they are not patch-tested to that food. The combination of both testing had a negative predictive value of 88% to 100% for all foods except milk (which was 40%), while the positive predictive value was >74% for the most common foods causing EoE. We have found that using the combination of skin prick test and atopy patch test for food

elimination can cause resolution of EoE symptoms and normalization of biopsies in about 80% of patients. ***Interestingly, the success rate of six-food elimination, oral viscous budesonide, and allergy testing–directed diet were all about the same 75% to 85%, giving a practitioner multiple choices on how to proceed.***

2. Treatment of aeroallergen-induced EGID

Studies suggest that pollen might have a role in EoE. However, there are no studies looking at treatment of pollen in EoE or whether use of immunotherapy might be helpful in EoE. The current consensus guidelines recommend management of all forms of atopy as well as the time of year for repeat endoscopies be taken into consideration.

3. Corticosteroid therapy

Systemic steroids were the first successful medical therapy used with resolution of symptoms and histology. However, their significant side effects preclude their long-term use. Currently, systemic steroids are indicated for short bursts when patients have severe symptoms, dyspha-gia, small-caliber esophagus, or strictures. The recommended dose of prednisone is 1 to 2 mg/kg/day (maximum 60 mg/day).

Topical steroids have been used in patients with EoE including aerosolized fluticasone or swallowed budesonide. There have been multiple reports reviewing their efficacy in children and adults, with improvement from 50% to 85% depending on the dose and age of child. However, when medications are stopped, esophageal eosino-philia returned in all studies. Compared to systemic steroids, topical steroids have less potential side effects but have not been studied over an extended period of time. The use of topical steroids is associated with local fungal infections 15% to 20% of the time. The current recommended doses from the 2011 consensus guidelines for swallowed fluticasone are 110 to 220 mg (swallowed) BID for children <6 years of age and 220 to 440 mg BID for children older than 6 years of age. Adult doses may be increased to a maximum of 880 mg BID. Recommended doses for viscous budesonide are 1 mg daily for children <10 years of age and 2 mg daily for children 10 years and older. Viscous budesonide was made by mixing each 0.5 mg budesonide respules with five packets of sucralose (Splenda).

4. Other medications: Cromolyn, leukotriene receptor antagonists (mon-telukast), and omalizumab did not show any histological improvement in open-label clinical trials. At this point, these drugs cannot be recommended for EoE.

5. Esophageal dilation

Stricture formation occurs in patients with EoE. Esophageal dilation is sometimes used with immediate and at times long-lasting relief. Earlier studies revealed significant side effect concerns including perforation and bleeding. However, recent studies showed that patients did improve and there was not significant perforation or bleeding, although retroster-nal chest pain did occur in many. Esophageal dilation does not address underlying inflammatory disease. In the 2011 consensus statement, patients with high-grade esophageal stenosis may benefit from dilation (as long as risk/benefits are discussed) in combination with dietary or medical management.

a. Treatment for EG

Treatment for eosinophilic gastroenteritis (EG) is specific for resolving the symptoms as opposed to focusing on the etiology, which is different than EoE. Following the

diagnosis of EG, any type of obstruction or perforation should be ruled out in order to eliminate the need for primary surgical intervention initially. The use of steroids tends to be successful in approximately 90% of cases. Steroids are commonly used as they are effective in reducing inflammation, but should not be used over long periods of time as a maintenance therapy due to side effects. Proton pump inhibitors, leukotriene antagonists (e.g., montelukast), immunosuppressive therapy, and mast cell stabilizers are additional classes of pharmaceutical agents that can provide relief in patients with EG, but their long-term efficacy has not been measured. The majority of patients, who may go on steroid therapy, tend to try an elimination diet. Food allergies should be identified, if any, and elimination diet can be trialed. However, in our experience, very few patients with EG respond to dietary therapy. Various treatments exist for EG and should be trialed to discover which therapy is most effective for each patient in terms of reducing symptoms, reducing the amount of eosinophils per high power field as indicated by biopsies, and preventing relapse.

b. Treatment for EC

Eosinophilic colitis has a bimodal distribution affecting young infants and young adults. There are no guidelines for the treatment of EC, and most of the recommendations come from case reports or case series. Non–IgE-mediated food allergies are the major cause of EC in infants. Cow's milk is the most common cause followed by soy as up to 30% of infants who react to cow's milk also react to soy. Both breastfed and bottle fed infants have EC. Removal of cow's milk and/ or soy (from infant and breastfeeding mother) leads to symptomatic improvement within a few days. Casein hydrolysate formulas have been used successfully in 80% of infants, whereas the remainder improves with elemental formulas. Because EC is thought to be a T cell driven, non–IgE-mediated condition, allergy skin prick testing or immunocap is typically negative. Patch testing has been used in our institution with varying success. The prognosis for these infants is good. Most will outgrow the condition by a year of age, if not, then by 3 years of age.

Young adults who present with EC may respond to an elemental diet or dietary restrictions, but not all do. The mainstay of therapy in adults is corticosteroids, with up to a 90% success rate. However, relapse is common when medication is tapered. Similar steroid-sparing medications used in EG have been tried with varying success in EC, including ketotifen, montelukast, and cromoglycate. Other immunosuppressants, such as 6-mercaptopurine and azathioprine, have been used for the more severe, refractory cases. More studies are necessary to guide therapy in patients with EC as well as EG.

c. Biologics for EGID

Humanized monoclonal antibody therapy blocking IL-5 (anti-IL-5) is currently under investigation for EoE. IL-5 is a key cytokine for the growth and differentiation of eosinophils. An open-label trial of mepo-lizumab (anti-IL-5) showed a significant improvement in 4 patients with biopsy improving from 150 to 40 eosinophils/HPF; however, this was still well above the normal level, zero eosinophils/HPF. These results have been only published in abstract form, showing an improvement in histological endpoints but not clinical improvement compared to placebo. One study found increased expression of TNF-α on epithelial cells from patients with active EoE. TNF-α is a known

proin-flammatory cytokine that may play a role in atopic disease, including asthma and EoE. In an open-label trial of infliximab (anti-TNF-α), there was no significant improvement in symptoms or histology in three adult patients with EoE, although one had a partial response.

IX. CONCLUSION

EGIDs are a group of disorders characterized by an inappropriate accumulation of eosinophils within the gastrointestinal tract. Their pathogenesis is most likely the result of local aberrant Th2 cytokines secreted in response to foods, aeroallergens, and/or as yet unidentified agents for at-risk patients. Most patients with EoE respond to elemental diet and steroids. However, both modes of therapy are undesirable long-term solutions for EGID. Therefore, many patients are treated with selective food elimination diets or swallowed "inhaled" corticosteroids as an off-label medication. In contrast to EoE, EC and EG are less understood and primarily treated with steroids. Further studies are needed in all EGIDs.

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18

Primary Immunodeficiency Diseases

Shradha Agarwal and Charlotte Cunningham-Rundles

Normal immune function is necessary for maintenance of health, though the first line of defense to infections are the natural physical barriers, skin and the epithelial surfaces of the respiratory, intestinal, and genital tracts, all of which serve to exclude such microbial invaders. Because the mucosal epithelium is a more permeable mechanical barrier than skin, other mechanisms in this location augment resistance, including ciliary clearance, mucus, low stomach pH, lysozyme, and lactoferrin. When infectious agents penetrate these tissues, other host factors, such as cytokines, complement, and phagocytic cells (neutrophils and macrophages) provide a second line of defense. At both the mucosal and systemic levels, a third line of immune defense includes the adaptive immune system: B lymphocytes, which produce antibodies, and T-cell– mediated immunity. Defects in components of these two systems lead to a spectrum of clinical manifestations, depending on the system(s) affected, the extent of impairment, and the compensatory mechanisms that can be recruited.

Deficiencies of the immune system can be congenital or acquired and are diagnosed in infants, children, or adults. Because primary immune (PI) defects have heterogeneous clinical manifestations, it can be difficult to determine which patients might benefit from an evaluation of the immune system and what tests are appropriate in each case. While patients with PI defects have infections with the same pathogens and may need repeated courses of antibiotics, the majority of patients seen in the office with recurrent infections are immunocompetent. This is especially the case in children since allergic rhinitis and asthma are among the most common diseases leading to repeated upper and lower respiratory tract infections. Other diseases, such as cystic fibrosis or the immotile cilia syndrome, may need to be considered to provide an accurate diagnosis and determine the correct therapy. Determining if an immune defect is likely to be present can be problematic, but some guidelines can aid the practicing clinician.

I. CLASSIFICATION OF PRIMARY IMMUNODEFICIENCY

The overall incidence of PI diseases is estimated at about 1 in 10,000, excluding selective IgA deficiency, which is much more common (see Section I.C); for unknown reasons, more than half of the reported immune defects (also excluding IgA deficiency) involve defects in antibody production. Despite the major advance in the molecular characterization of these diseases, many patients remain undiagnosed or are diagnosed after severe complications have already occurred, making early recognition important. To evaluate a patient for immunodeficiency, a basic understanding of the immune system is useful. The **International Union of Immunologic Sciences (IUIS)** has compiled a catalog of the known defects of the immune system that is periodically updated. An overview of major immunodeficiency syndromes, divided by type, is given in Table 18-1. Within these major headings, recognized clinical syndromes can be grouped, according to the predominant mechanism(s) that is defective.

Table 18-1 Types of Primary Immunodeficiency Syndromes

	Clinical Findings	Lab Findings	Inheritance	Molecular Defects

Predominately antibody deficiencies				
Agammaglobulinemia	Recurrent and severe bacterial infections, enteroviral infections, absent lymphoid tissue, autoimmunity	Absent IgM, IgG, and IgA; B cells <1% of lymphocytes; absent specific antibody response	XL and AR	X-linked (BTK), autosomal recessive (μ heavy chain, λ5, Igα, Igβ, BLNK)
Common variable immunodeficiency (CVID)	Variable phenotype: Recurrent bacterial infections, autoimmune disease, lymphoproliferative and/or granulomatous disease	Low IgG and IgA and/or IgM; absent specific antibody response; normal or decreased B-cell numbers; variably decreased T-cell responses	Variable	Mutations in *ICOS, CD19,* CD20, CD81, *TNFRSF13B, TNFRSF13C, mostly* unknown
Hyper-IgM syndrome	Recurrent bacterial infections, opportunistic infections, neutropenia, autoimmune disease, sclerosing cholangitis	Low IgG and IgA; normal or increased IgM; normal or increased B-cell numbers; decreased T-cell responses in CD40L/CD40 deficiency	XL and AR	Mutations in *CD40L, CD40, AICDA, UNG*
Selective IgA deficiency	Usually asymptomatic; some with recurrent bacterial infections, atopy, autoimmunity, and gastrointestinal disorders	Low/absent IgA; normal IgG and IgM; impaired specific antibody responses in some patients	Variable	Unknown
Specific antibody deficiency	Recurrent upper respiratory tract infections	Normal IgG, IgM, and IgA levels; impaired specific antibody response (polysaccharides); normal B-cell numbers	Variable	Unknown
IgG subclass deficiency	Usually asymptomatic, some with recurrent bacterial infections, atopy, and autoimmunity	Low levels of one or more IgG subclasses; normal total IgG, IgA, and IgM; normal B-cell numbers; impaired specific antibody responses in some patients	Variable	Unknown
Transient hypogammaglobulinemia of infancy (THI)	Recurrent upper respiratory tract infections	Low IgG levels with variably low IgA and rarely low IgM; normal specific antibody responses in most; normal B-cell numbers	Variable	Unknown
Combined T- and B-Cell immunodeficiencies				
T−B+NK− SCID	Failure to thrive, chronic diarrhea, oral thrush, recurrent and severe bacterial, viral, and/or fungal infections early in life	Decreased serum immunoglobulins; normal or increased B-cell numbers; markedly decreased T-cell numbers	XL or AR	Defects in JAK3, γ-chain of receptors for IL-2, IL-4, IL-7, IL-9, IL-15, IL-21
T−B−NK− SCID	Failure to thrive; chronic diarrhea; recurrent and severe bacterial, viral, and/or fungal infections early in life; costochondral junction flaring; neurologic features; hearing impairment; lung and liver manifestations	Decreased serum immunoglobulins; absent T- and B-cell numbers	AR	Defects in adenosine deaminase
T−B−NK+ SCID	Failure to thrive, chronic diarrhea, oral thrush, recurrent and severe bacterial, viral, and/or fungal infections early in life; those with Omenn's syndrome have erythroderma, adenopathy, hepatosplenomegaly, eosinophilia; those with Cernunnos have microcephaly, growth retardation, radiation sensitivity	Decreased serum immunoglobulins; markedly decreased T- and B-cell numbers	AR	Defect in RAG 1/2, Artemis, ligase 4, Cernunnos
T−B+NK+ SCID	Failure to thrive, chronic diarrhea, oral thrush, recurrent and severe	Decreased serum immunoglobulins; normal or increased B-cell	AR	IL-7 receptor α-chain

	bacterial, viral, and/or fungal infections early in life	numbers, markedly decreased T-cell numbers		
CD8+CD4–B+NK+ SCID	Failure to thrive, recurrent and severe bacterial, viral, and/or fungal infections early in life	Normal or decreased serum immunoglobulins; normal B-cell numbers; decreased CD4 cells; normal CD8 cells	AR	Mutations in MHC class II proteins
CD8–CD4+B+NK+ SCID	Failure to thrive, recurrent and severe bacterial, viral, and/or fungal infections early in life	Normal serum immunoglobulins; normal B-cell numbers; decreased CD8, normal CD4 cells	AR	Defects in *ZAP70*
Other immunodeficiencies				
DiGeorge's syndrome	Conotruncal malformation; hypoparathyroidism; abnormal facies; absent thymus in complete forms	Immunoglobulins usually normal though occasionally IgE elevated and IgA reduced; normal B-cell numbers; low to absent T-cell numbers in complete forms; varying degrees of T-cell function according to thymic deficiency	De novo or AD	Evidence that point mutations in the *TBX1* gene is involved
Hyper-IgE syndromes	Distinctive facial features (broad nasal bridge), eczema, osteoporosis, fractures, scoliosis, delayed shedding of primary teeth, bacterial infections (skin and pulmonary abscesses), susceptibility to intracellular bacteria, fungi, and viruses	Elevated IgE >2,000 IU/mL; eosinophilia in some	AD or AR	Mutations in *STAT3, TYK2, DOCK8*
Chronic mucocutaneous candidiasis	Chronic mucocutaneous candidiasis, autoimmunity	Normal serum immunoglobulins; normal B-cell numbers; normal T-cell numbers (defect of Th17 cells in CARD9 deficiency)	AD, AR, sporadic	Mutations in *CARD9* in one family with AR inheritance; AIRE defects in some; unknown in others
Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy (APECED)	Autoimmune disease (usually parathyroid and adrenal), candidiasis, dental enamel hypoplasia	Normal T- and B-cell numbers; organ-specific autoantibodies	AR	Defects in *AIRE*
X-linked lymphoproliferative (XLP)	Clinical and immunologic abnormalities triggered by EBV infection; hepatitis, aplastic anemia, lymphoma	Normal or low immunoglobulins; normal T-cell numbers; normal or reduced B-cell numbers	XL	Defects in *SH2D1A, XIAP*
Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX)	Autoimmune diarrhea, early-onset diabetes, thyroiditis, hemolytic anemia, thrombocytopenia, eczema	Elevated IgA and IgE; normal B-cell numbers; lack of CD4+CD25+FOXP3+ regulatory T cells; eosinophilia	XL	Defects in *FOXP3*
Ataxia-telangiectasia	Ataxia, telangiectasia, pulmonary infections, lymphoreticular and other malignancies, increased x-ray sensitivity, chromosomal instability	Often low IgA, IgE, and IgG subclasses; increased IgM monomers; antibodies variably decreased; normal B-cell numbers; progressive decline in T-cell numbers; increased alpha fetoprotein	AR	Mutations in *ATM*
Autoimmune lymphoproliferative syndrome (ALPS)	Splenomegaly, adenopathy, autoimmune blood cytopenias, defective lymphocyte apoptosis	Increased double-negative T cells; normal B-cell numbers	AD or AR	Defects in *TNFRSF6, CASP10, CASP8, NRAS*
Wiskott-Aldrich syndrome	Thrombocytopenia, eczema, autoimmune disease, bacterial and viral infections, lymphoreticular malignancy	Decreased IgM; often increased IgA and IgE; antibody response to polysaccharides decreased; normal B-cell numbers; progressive decrease in T-cell numbers with abnormal lymphocyte responses to anti-CD3	XL	Mutations in *WAS*
Chronic granulomatous disease (CGD)	Diarrhea, colitis, hepatomegaly, splenomegaly, granulomas, abscess, skin infections, recurrent bacterial and fungal infections *(Staphylococcus aureus and Aspergillus)*	Defective oxidative burst by DHR or NBT equivalent	XL or AR	Mutations in *CYBA, CYBB, NCF1, NCF2*

Abbreviations: AD, autosomal dominant inheritance; AICDA, activation-induced cytidine deaminase; AIRE, autoimmune regulator; AR, autosomal recessive inheritance; ATM, ataxia-telangiectasia mutated; BLNK, B-cell linker protein; BTK, Bruton's tyrosine kinase; CARD9; caspase recruitment domain–containing protein 9; CASP, caspase; CYBA, cytochrome b alpha subunit; CYBB, cytochrome b beta subunit; DHR, dihydrorhodamine; DOCK8, dedicator of cytokinesis; FOXP3, forkhead box rotein 3; ICOS, inducible costimulator; JAK3, Janus kinase 3; MHC II, major histocompatibility complex class II; NBT; nitroblue tetrazolium; NRAS, neuroblastoma RAS protein; RAG, recombination activating gene; SH2D1A, SH2 domain protein 1A; STAT3, signal transducer and activator of transcription 3; TBX1, T-box 1; TNFRSF, tumor necrosis factor receptor superfamily; TYK2, tyrosine kinase 2; UNG, uracil-DNA glycosylase;

WAS, Wiskott-Aldrich syndrome; XL, XIAP, X-linked inhibitor of apoptosis; X-linked inheritance; ZAP70, zeta chain–associated protein kinase, 70kD

A. Combined cellular and antibody (T- and B-cell) deficiencies. The most severe and characteristic form of combined immune defects are the severe combined immunodeficiencies (SCID), a group of defects characterized by significant T-cell defects and B-cell dysfunction (Table 18-2). Since combined immune deficiencies also impair the production of antibodies, multiple severe infections are likely to occur in the first few months of life. Most infants have decreased numbers of T lymphocytes, hypogammaglobulinemia, and loss of antibody production. Another well-known combined defect is Wiskott-Aldrich syndrome, found in males, commonly associated with thrombocytopenia and eczema.

Table 18-2 Lymphocyte Phenotypes Associated with Various Forms of SCID

Phenotype	Form of SCID
T–B–NK–	ADA
T–B+NK–	JAK3, γ-chain of receptors for IL-2, IL-4, IL-7, IL-9, IL-15, IL-21
T–B–NK+	RAG 1/2, Artemis, ligase 4, Cernunnos
T–B+NK+	IL-7 receptor α-chain
CD8+CD4–B+NK+	MHC class II
CD8–CD4+B+NK+	ZAP70

Abbreviations: ADA, adenosine deaminase; JAK3, Janus kinase 3; RAG, recombination activating gene; ZAP70, zeta chain-associated protein kinase, 70kD.

B. Cellular deficiency (T-cell) disorders. DiGeorge's syndrome is the best characterized T-cell defect, and most DiGeorge patients have cardiac abnormalities and hypocalcemia, though the syndrome can be quite heterogeneous with only subtle defects such as cleft palate in some. Although it is operationally useful to classify DiGeorge's syndrome as an isolated T-cell disorder, when thymic development and T-cell function is markedly impaired, antibody formation is also deficient.

C. Antibody deficiency (B-cell) disorders are the most common PI defects. **Selective IgA deficiency** is the most common, of these, and has an incidence of approximately 1 in 500 to 1,000 in patients of European origin. While most of these individuals do not have medical problems, allergies, asthma, and various autoimmune diseases (e.g., celiac disease, thyroiditis) are more common in patients with selective IgA deficiency. More medically important are the defects in which serum immunoglobulin (Ig) levels (IgG, IgA, and/ or IgM) may be markedly decreased or completely absent. The best known of these defects is **Bruton's X-linked agammaglobulinemia (XLA)**, which is almost always diagnosed in males in early childhood. Aside from this B-cell defect, the majority of patients with significant antibody defects such as **common variable immune deficiency (CVID)** are adults when the defect is recognized. Of uncertain incidence, antibody deficiency with normal serum immunoglobulin concentrations may also occur. Antibody deficiency in these cases can be broad (both antibody to protein and polysaccharide antigens are absent) or more restricted (e.g., to carbohydrate bacterial capsular antigens).

D. Complement deficiencies account for a small percentage of primary immunodeficiencies. The most commonly diagnosed is deficiency of the C1 inhibitor, which results in recurrent attacks of

angioedema (this is covered in Chapter 12, Urticaria and Angioedema). As complement activation leads to appropriate opsonization of microbes, this loss can result in inadequate coating of bacteria with antibody, reduced or absent phagocytosis, or ineffective lysis of microorganisms, leading to severe bacterial infections such as meningitis, sepsis, or organ abscesses. Defects in the early components of the classical complement pathway (C1, C2, C4) typically manifest as systemic lupus erythematosus– like autoimmune manifestations, but recurrent sinopulmonary infections also occur with C2 deficiency. C2 deficiency is the most common defect in subjects of European descent and estimated to occur in 1:10,000 subjects. Defects in the late components of complement (C5 to C9), necessary for generation of the membrane attack complex (MAC), result in susceptibility to infections with *Neisseria meningitidis,* sepsis, or gonococcal arthritis. Alternative complement pathway defects, such as factors B, D, and properdin, can also lead to Neisseria infections.

E. Phagocytic disorders. Defects of neutrophils can be categorized as due to impaired numbers, loss of chemotaxis, phagocytosis, and/or intracellular killing. The commonest defect is neutropenia, often discovered during the course of an evaluation of bacterial infections or inflammation of the mucus membranes or gingiva. Severe neutropenia, defined as absolute neutrophil count below 500 cells/μL, occurs in **Kostmann's syndrome** (congenital neutropenia). This needs to be distinguished from autoimmune neutropenia, which also occurs in infancy but spontaneously resolves by age 5 or 6. **Cyclic neutropenia** is an autosomal dominant inherited disease characterized by neutropenia that recurs every 14 to 35 days (the majority occur in a 21-day cycle) for 3 to 5 consecutive days per cycle. Most cases are mild and benign but occasionally severe with life-threatening infection. Another well-characterized neutrophil defect is **chronic granulomatous disease (CGD)** in which there is loss of the genetic mechanisms leading to the oxidative burst, resulting in defective intracellular bacterial killing, abscess formation, and, over time, organ damage. Another genetic defect is **leukocyte adhesion deficiency (LAD)**, in which leukocytes fail to attach to endothelial cell surfaces due to mutations in the CD18 integ-rin; here, leukocytes are unable to migrate into tissues to eliminate bacteria.

F. Other defects of innate immunity. Mutations in genes encoding the **toll-like receptors (TLR)** result in a selective susceptibility to pathogens. For example, patients with mutations in the genes encoding *IRAK4* and *MYD88* are susceptible to severe and invasive pyogenic infections early in life. The infections become less frequent after the first 10 years of life, but mortality is high in the first decade. Heterozygous mutations in *TLR3* and biallelic mutations in *UNC93B* have been also identified in infants with selective susceptibility to herpes simplex encephalitis, with reduced production of type 1 interferon (IFN). Defects of the IL-12/IFN-γ pathway (IL-12 p40 subunit, IL-12 receptor **(3**1 chain, chains of the IFN-γ receptor, and STAT1 gene) are associated with susceptibility to mycobacterial disease. Mutations in the *IKBKG* gene, which encodes **NF-kB essential modulator (NEMO),** a regulatory factor of the nuclear factor κB signaling pathway, lead to an X-linked disorder called **NEMO deficiency** characterized by ectodermal dysplasia, bacterial infections, and increased susceptibility to mycobacterial disease.

G. Disorders of immune dysregulation. A number of the components of the immune system are required for appropriate immune regulation. Because of this, it might not be surprising that some

forms of PI are associated with immune dysregulation and autoimmunity. During the early development of the immune system, the first step in the exclusion of autoimmunity occurs in the thymus, with deletion of autoreactive T-cell clones, a process called central immune tolerance. Mutations of the *AIRE* gene, which is essential for the deletion of T-cell clones that recognize self-antigens, lead to **autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy syndrome (APECED)**. In this syndrome, autoimmune manifestations such as hypoparathyroidism and adrenal insufficiency along with chronic mucocutaneous candidiasis occur. Mutations of the *FOXP3* gene, which is essential for the development of T-regulatory cells, lead to **immune dysregulation**, **polyendocrinopathy**, **enteropathy**, **X-linked (IPEX) syndrome**. The IPEX syndrome in males incorporates severe enteropathy, eczema, and insulin-dependent diabetes. Mutations of Fas (CD95), which is involved in intracellular signaling pathways essential for activation of caspases and cell death, are the predominant cause of **autoimmune lymphoproliferative syndrome (ALPS)**. This constellation is characterized by striking lymph-adenopathy, hepatosplenomegaly, and autoimmune cytopenia.

II. CLINICAL FINDINGS IN IMMUNODEFICIENCY DISORDERS

The most frequent clinical indicator of an immune defect is the occurrence of "too many infections." This is the main manifestation of infants and children with PI and presents a significant challenge to the physician because infections are so common in normal childhood. When frequent and prolonged infections are coupled with failure to thrive, or if unusual infections appear, an evaluation of the immune system is in order. For older children and adults, frequent or unusual infections may also suggest an immune defect, but in these age groups, other medical indications such as autoimmunity, enlarged lymph nodes or spleen, and weight loss, among other signs, may also suggest the presence of an immune defect. For all age groups, a confirmed report of an immunodeficiency disease occurring in a sibling or first-degree relative should also prompt careful clinical assessment and laboratory investigation, even without a history of severe or unusual infections. Some of the more common clinical findings of PI are listed in Table 18-3.

Table 18-3 Clinical Features of Immunodeficiency

Usually present	Recurrent upper respiratory infections—sinusitis, bronchitis, pneumonia, otitis media
	Severe bacterial infections
	Persistent infections with incomplete or no response to therapy
Often present	Failure to thrive or growth retardation for infants or children
	Weight loss in adults
	Intermittent fever
	Infection with unusual organisms
	Skin lesions, such as rash, seborrhea, pyoderma, necrotic abscesses, alopecia, eczema, telangiectasia
	Recalcitrant thrush; cutaneous or mucosal
	Autoimmune disease such as autoimmune thrombocytopenia, hemolytic anemia, rheumatologic disease, alopecia, thyroiditis, pernicious anemia, vitiligo
	Diarrhea and malabsorption
	Hearing loss due to chronic otitis
Occasionally present	Sclerosing cholangitis
	Lymphadenopathy
	Hepatomegaly and/or splenomegaly
	Severe viral disease (e.g., varicella or herpes simplex)
	Chronic encephalitis
	Recurrent meningitis
	Pyoderma gangrenosum
	Adverse reaction to vaccines
	Delayed umbilical cord detachment
	Chronic stomatitis or peritonitis
	Bronchiectasis
	Granulomas
	Lymphoid malignancies
	Chronic conjunctivitis

(Adapted from Stiehm ER, Ochs HD, Winkelstein JA. Immunodeficiency disorders: general considerations. *Immunologic disorders in infants and children*, 5th ed. Philadelphia, PA: Elsevier Saunders, 2004:289–355.)

A. History

1. **Sinopulmonary infections** are a common symptom of most PI diseases. In most cases, sinopulmonary infections, including recurrent otitis media, sinusitis, bronchitis, and pneumonia, are due to common respiratory bacterial pathogens, such as *Streptococcus pneumoniae*, *Haemophilus influenzae* (often untypeable), *Moraxella catarrhalis*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. Although frequent (6 to 10 per year) upper respiratory infections are common in normal young children, especially if there is exposure to older siblings or to other children (e.g., daycare centers) or coexisting respiratory allergies, there are some distinguishing characteristics of infections that can suggest abnormal host resistance (such as the presence of fever, more purulent secretions, lack of clear allergy symptoms, lymphadenopathy, positive family history for immunodeficiency, or need for frequent antibiotics). These infections can become chronic and lead to complications, such as perforated tympanic membranes, otitis media with mastoiditis, restrictive lung disease, or bronchiectasis.
2. **Other bacterial infections** (e.g., deep infections such as cellulitis, osteomyelitis, meningitis, or sepsis). Although severe infections can occur in healthy individuals, two severe infections of this kind suggest the possibility of PI. A patient presenting with recurrent abscesses caused by gram-negative organisms such as *Escherichia coli, Burkholderia cepacia*, *Serratia*, or *Klebsiella* can have abnormal phagocytic function. Recurrent neisserial infections characterized by sepsis suggest a deficiency of terminal

complement component.

3. **Viral infections,** for example, respiratory syncytial virus (RSV), adenovirus, parainfluenza, cytomegalovirus (CMV), can be severe and life threatening in infants with SCID. Shingles infections in children or young adults can occur in those with either antibody or T-cell defects. Devastating herpes simplex encephalitis occurs in infants with selected TLR defects. Children with X-linked lymphoproliferative disease are typically well until developing an Epstein-Barr virus (EBV) infection.
4. **Other specific organisms (opportunistic, parasitic, fungal).** Infections with opportunistic organisms, such as *Pneumocystis carinii*, *Aspergillus fumigatus*, *Giardia lamblia*, cryptosporidia, atypical mycobacteria, or *Candida albicans* (thrush), suggest cell-mediated dysfunction. (HIV infection should be excluded.) Uncontrolled replication of bacilli Calmette-Guerin (BCG) following vaccination is a classic presentation of SCID in areas that administer this vaccine. Infections with *Aspergillus* spp. or *Candida* spp. are also commonly found in individuals with phagocytic disorders.
5. **Autoimmune diseases** are seen in up to 25% of patients with primary antibody deficiency; autoimmune hemolytic anemia and autoimmune thrombocytopenia are the most common, but other autoimmune conditions such as rheumatoid arthritis, pernicious anemia, thyroiditis, and vitiligo among others may occur. Patients lacking one of the early complement components are susceptible to lupus-like illnesses.
6. **Gastrointestinal disease.** Chronic or prolonged diarrhea, with or without evidence of malabsorption or weight loss, is frequently present in all types of immunodeficiency disorders. Infectious etiologies, such as *Giardia lamblia*, *Campylobacter*, *Cryptosporidium*, enteropathic *Escherichia coli*, *Helicobacter pylori*, or viruses (e.g., rotavirus and cytomegalovirus), occur. Other causes of diarrhea include intestinal lymphoid nodular hyperplasia, disaccharidase deficiency, sprue-like (celiac and nonceliac) syndrome, inflammatory conditions resembling Crohn's disease, or intestinal lymphoma. Any patient with gastrointestinal symptoms unresponsive to conventional therapies should be evaluated for an immunodeficiency.
7. **Failure to thrive** often occurs in infants and children, but its absence does not exclude an immunodeficiency. Failure to thrive is particularly frequent in cell-mediated immunodeficiency disorders, especially when diarrhea develops. In adults, weight loss or loss of subcutaneous fat is a more common manifestation.
8. **Surgical history.** Sinus surgery may have been performed for recurrent infections. Other surgeries may have included incision and drainage, tonsillectomy and adenoidectomy, lymph node biopsies, thymomectomy, lobectomies, and intestinal biopsies. A retrospective pathology review of lymphoid tissue (tonsils, adenoids, and intestine) can help to evaluate the absence of germinal centers and plasma cells, or both which suggests B-cell disorders such as XLA, CVID, and hyper-IgM.
9. **Family history.** Table 18-1 lists the inheritance patterns of selected primary immunodeficiency disorders. As illustrated, some of these disorders are inherited as either X-linked or autosomal recessive inherited traits. A history of consanguinity should be sought and, if possible, a family genealogic tree constructed. Important clues in other

family members include fetal death, death of a child with recurrent infections in early infancy, autoimmune disorders, and lymphoreticular malignancies.

B. Physical Examination

The physical examination can reveal pertinent clues to the nature of an immune defect, though a normal examination does not exclude an underlying PI. The physical examination should include the following:

1. **Height and weight.** Failure to thrive in children is a common feature of cell-mediated immune deficiencies, especially when associated with chronic diarrhea. An active, well-nourished, well-developed child is not as likely to have a serious (T- and B-cell) immunologic deficiency, although children with B-cell immune deficiencies can grow normally. For children, growth charts can serve as a guide to the effectiveness of therapy. An apparent appearance of normality can be misleading because a substantial immune defect can be documented in adults who look perfectly normal.
2. **Oral examination.** Periodontitis can be a sign of neutrophil disorders. Defects of the CD18 integrin, leading to leukocyte adhesion deficiency, lead to early loss of most teeth. Mucosal ulcerations of the tongue or oral mucosa appear in many immunodeficiency syndromes. Retention of primary teeth is an indicator of the hyper-IgE syndrome. Although candidiasis involving the oral pharynx may be present in young infants, it is not normally seen after about 1 year of age in a healthy infant. It is a common presentation in cell-mediated immunodeficiencies (e.g., SCID, IPEX, APECED, DiGeorge's syndrome, and Wiskott-Aldrich syndrome). Several features distinguish candidiasis in the immunocompromised host, including lack of predisposing conditions such as concomitant antibiotic or corticosteroid usage and breast-feeding, persistence of candidal involvement in the older infant, resistance to appropriate antifungal therapy, reappearance after appropriate treatment, presence of candidal esophagitis, and/or persistent cutaneous involvement.
3. **Eyes, ear, nose, and throat.** Purulent discharge from the ear, with or without tympanic membrane perforations and scarring, is a frequent finding. Sinus tenderness, with or without purulent rhinitis, is common. Chronic conjunctivitis due to nontypable *H. influenzae* and other polysaccharide-encapsulated bacteria is often present, especially in the antibody deficiency syndromes. Dysmorphogenesis of the third and fourth pharyngeal pouches in DiGeorge's syndrome also results in bifid uvula, short philtrum, hypertelorism, mandibular hypoplasia, and low-set, often notched ears. Small-vessel abnormalities over the bulbar conjunctivae (called telangiectasia) associated with cerebellar ataxia are characteristic of ataxia-telangiectasia (AT). Hypertelorism, epicanthal folds, and a flat nasal bridge can be seen in patients with immunodeficiency with centromeric instability and facial anomalies (ICF).
4. **Lymphoid tissue.** Small or absent peripheral lymph node tissues can be found in both T- and B-cell immunodeficiency syndromes. However, as a result of chronic infections, lymphadenopathy can result from antigen stimulation and accompanying immune dysregulation. In XLA, the tonsils, adenoids, and peripheral lymph nodes are small due to the absence of germinal centers. Tonsils and lymph nodes in CVID are either normal in size or enlarged, and splenomegaly occurs in approximately 25% of patients. Lymphoid

hyperplasia is also seen in hyper-IgM patients. In the autoimmune lymphoproliferative syndrome (ALPS), defective apoptosis of lymphocytes causes lymphoproliferation, and patients develop massive lymphadenopathy and hypersplenism.

5. **Pulmonary.** Clubbing of the fingers or chest examination demonstrating increased anterior to posterior diameter, persistent crackles, wheezes, or rhonchi suggest the complications of chronic pulmonary disease (e.g., bronchiectasis) most commonly associated with the antibody deficiency states, XLA and CVID.
6. **Cardiac.** Developmental embryologic abnormalities of the thymus in DiGeorge's syndrome can result in structural abnormalities of the heart such as **tetralogy of Fallot**, **ventricular septal defect (VSD)/atrial septal defect (ASD),** and **pulmonic artery atresia/stenosis**. Loud pulmonic heart sounds with a right ventricular heave are a sign of pulmonary hypertension, indicating pulmonary damage has occurred.
7. **Gastrointestinal.** Abdominal examination should focus on signs of weight loss, palpation for enlarged liver or spleen, and symptoms of liver dysfunction such as blood flow patterns on the abdomen, jaundice, and mental status changes. Inflammatory bowel–like disease, sprue-like disease, atrophic gastritis, splenomegaly, and nodular lymphoid hyperplasia can be seen in CVID. Sclerosing cholangitis can occur in hyper-IgM syndrome. CGD patients can develop obstruction in the GI tract from granulomatous infiltration.
8. **Musculoskeletal.** Arthritis is a frequently associated manifestation in patients with antibody deficiency disorders, but it may appear in combined immune defects such as Wiskott-Aldrich syndrome and in hyper-IgM syndrome. Scoliosis, bone fractures following minimal trauma, and joint hyperextensibility are characteristic of the hyper-IgE syndrome in which STAT3 mutations occur.
9. **Skin/Nails.** Skin lesions are commonly found in patients with T-cell abnormalities. Severe diaper rash is common in infants with combined T- and B-cell defects or T-cell defects. Weeping scalp seborrheic dermatitis is also common in (especially young) patients with hyper-IgE syndrome and the autosomal recessive form of SCID called Omenn's syndrome associated with mutations in the recombination activating genes RAG1 and RAG2. Children with Omenn's syndrome have early onset of a diffuse, exudative erythroderma with eosinophilia and elevated IgE. Ectodermal dysplasia in NEMO is characterized by conical or absent teeth, fine sparse hair, and hypohidrosis due to decreased sweat glands. Nail infections are common in mucocutaneous candidiasis, hyper-IgE syndrome, and APECED. Cutaneous abscesses can occur, especially in neutrophil disorders. This includes rectal abscesses and the presence of previously healed abscesses or fistulae. Delayed umbilical cord detachment and poor wound healing is observed in leukocyte adhesion defects secondary to CD11/CD18 integrin deficiency (e.g., LAD I). Petechiae may be visible in Wiskott-Aldrich syndrome. A lupus-like malar rash can be seen in deficiencies of the early components of the classical complement pathway.

III. EVALUATION OF THE IMMUNE SYSTEM

When an immune defect is suspected, the immediate questions to be addressed are what part(s) of the immune system need to be investigated? What tests are needed? How extensive do these

investigations need to be? Appropriate testing will provide diagnostic information and also guide the decision regarding therapy. **The selection of immunologic tests must be guided by clinical suspicion based on the clinical history and physical examination.** The evaluation of the immune system is best approached in stages, performing the basic screening tests first and turning to more advanced testing as indicated. An overview of this staged approach is given in Table 18-4.

Table 18-4 Staged Approach to Evaluation of the Immune System

Stage Ia of immunologic tests
History and physical examination, height/weight
CBC and differential with morphologic analysis
Quantitative immunoglobulin levels
HIV testing as required
Stage Ib of immunologic tests
Specific antibody responses (tetanus, diphtheria, MMR, varicella, pneumococcal)
Pre-/postimmunization response to protein and/or carbohydrate antigens
Isohemagglutinin
IgG subclasses
Stage II of immunologic tests
Enumeration of blood cell populations—total T and B cells, T-cell subsets, NK cells
In vitro functional studies—mitogens and antigens
Complement screening CH50, C3, C4
Phagocyte studies (oxidative burst by DHR or NBT equivalent)
Stage III of immunologic tests
Individual complement levels and functional assays
Flow cytometric evaluation of intracellular or surface protein markers
Genetic studies
Enzyme measurements (ADA, PNP, G6PD)
DNA analyses
Cytokine production/receptor studies

A. Initial Screening Investigations

1. **Previous medical records and a complete blood count and differential.** The initial visit should include obtaining all the previous medical records, including pathology reports or slides, and results of previous cultures and radiologic studies. Aside from the initial history and physical examination, including measuring the height and weight, the first immune test is the complete blood count. A white blood count and differential will provide information on the number of each cell type. **The absolute lymphocyte count must be compared with age-matched control ranges for proper interpretation.** Severe lymphopenia in an infant ($<2{,}000/mm^3$) is a critical finding that, if confirmed on a repeat test, should prompt an immediate immune evaluation. A diagnosis of cyclic neutropenia will require obtaining absolute neutrophil counts two to three times a week for at least 4 to 6 weeks. Patients with Wiskott-Aldrich syndrome may have thrombocytopenia and small platelets. Where appropriate, HIV should be excluded.

2. **Pulmonary function.** Immune deficiency, especially if it has persisted for some time, can affect lung function. Patients with both T- and B-cell defects are subject to recurrent and chronic pulmonary infections, resulting in bronchospasm, restrictive or obstructive disease, or combinations of these abnormalities. Complete lung function with volumes, flows, and diffusion capacity should be tested, even if the chest x-ray is normal. Sweat

chloride determinations or genetic studies should be done when cystic fibrosis is considered or suspected.

3. Serum immunoglobulins. Because antibody deficiency diseases are more common than other immune defects, initial emphasis should be placed on the investigation of immunoglobulins and antibody production. Quantitative immunoglobulins give the serum levels of IgG, IgA, IgM, and IgE. Because immunoglobulin values increase up until about age 6, comparison to age-matched controls is necessary for correct interpretation. IgE levels can not only help to distinguish between allergic and immunodeficiency disease but also indicate the immune deregulation of hyper-IgE syndrome or forms of SCID in which IgE levels are maintained (Omenn's syndrome).

4. Antibody production. When a B-cell immunodeficiency is suspected, antibody responses to both protein and polysaccharide antigens are examined to most accurately assess B-cell function. This is particularly important if treatment with immunoglobulin is being considered and must be done prior to administering immunoglobulin (i.e., intravenously or subcutaneously administered immunoglobulin). If the use of this therapy is later questioned, the immunoglobulin will need to be stopped for 5 to 6 months before reassessing antibody production.

a. **Antibody responses to protein antigens.** The first step in assessing IgG antibody responses to protein antigens is to determine antibody titers to diphtheria and tetanus toxoids pre- and postimmunization (4 weeks). Antibody responses following immunization to killed poliomyelitis and hepatitis B vaccines can also be used. If the child or adult has received the usual immunizations (measles, mumps, rubella, varicella) in the past, antibody titers for these vaccine antigens can be quantified. Nonproductive levels may indicate a missed immunization; therefore, if the child has not been immunized, or for adults in whom more time has elapsed since vaccination, a measurement of the response 4 to 6 weeks after booster vaccine administration should be performed. No consensus exists on how best to interpret each response; in general, an increase of fourfold or more over baseline and/or establishing protective levels of antibody signify an adequate response. Patients with high preimmunization titers may not demonstrate a fourfold increase yet are still considered immunocompetent.

b. **Antibody responses to polysaccharide antigens.** To measure antibody responses to polysaccharide antigens in children older than 2 years of age, the pneumococcal vaccine, free of carrier proteins, is used. Antibody titers are determined before (preimmunization) and 4 to 6 weeks postimmunization, ideally at the same clinical laboratory. Measurement of antibody titers to 12 to 14 different serotypes will give more useful information than examining only four or seven responses. Guidelines for adequate responses are usually a postimmunization serum antibody concentration of 1.3 μg/mL or greater or at least a fourfold over baseline. However, even people with normal immunity may not respond to all serotypes; in one study, 11% of healthy adults responded to only 50% of the serotypes tested. Therefore, one must decide what response is satisfactory in a given patient. Antibody responses to carbohydrate antigens are typically poor in children younger than 2 years old and may be depressed up to 5 years of age. Polysaccharide vaccines are not useful in young infants because

most children born after 2000 have been vaccinated with the conjugated vaccine (Prevnar), which is more immunogenic than the unconjugated vaccine.

A polysaccharide vaccine for meningococcus is also available and can be used for the measurement of a polysaccharide response though the interpretation of the response is not yet well established.

c. Isohemagglutinins are naturally formed antibodies that cross-react with A or B blood group erythrocyte antigens. Thus, anti-A or anti-B blood group substance can be used as a test of antibody production for subjects who are blood group A (who have anti-B antibody), or for those who are blood group B (who have anti-A), or for blood group O subjects (who have both). These antibodies develop in subjects older than the age of 2 years and are usually found in a titer of 1:16 or greater.

5. Immunoglobulin G subclasses. IgG consists of four subclasses, IgG1 to IgG4, which make up approximately 70%, 20%, 7%, and 3% of total IgG levels, respectively. Thus, deficiencies in IgG1 or IgG2 are more likely to cause low serum IgG levels because these are the major components. The significance of isolated IgG subclasses is controversial. Measurement of IgG subclasses may be indicated in patients with repeated bacterial sinopulmonary infections who have normal or mildly subnormal IgG levels or selective IgA deficiency. However, determining functional antibody responses to polysaccharide antigens, such as *S. pneumoniae*, is essential and more clinically relevant. The actual significance of IgG subclass deficiency requires documenting an abnormality in antibody testing prior to initiating Ig therapy.

B. Second-Level Measurements

1. Fecal alpha-1 antitrypsin, urinary protein, serum albumin. Hypogammaglobulinemia can also result from protein loss, excluded by measuring serum albumin and urinary protein levels, whereas enteral loss can be excluded by measurement of stool alpha-1 antitrypsin.

2. T, B, and natural killer (NK) cell enumeration. Analysis of lymphocyte phenotypes using monoclonal antibodies and flow cytometry will identify a large number of cell surface proteins, some of which are unique to certain lymphocyte populations. Specific antibodies can be used to identify T and B cells, subpopulations of T cells, natural killer (NK) cells, and monocytes/macrophages (Chapter 20, Diagnostic Immunology). PI diseases can result in defective generation of T cells ($CD3^+$ cells) or low numbers of $CD4^+$ and/or $CD8^+$ T cells. If an immune defect is suspected, the absolute numbers of $CD3^+$, $CD4^+$, and $CD8^+$ cells are determined and compared to the laboratory-established normal controls of similar age. Sixty-five to seventy percent of peripheral lymphocytes are T ($CD3^+$) cells, about 60% are $CD4^+$ cells, and the remainder are $CD8^+$ T cells. About 10% to 20% of peripheral blood lymphocytes are B cells ($CD19^+$ or $CD20^+$) in older children and adults, but there are somewhat higher numbers in young infants. Monocytes ($CD16^+$) and NK cells ($CD56^+$) are also identified by specific markers and form the remaining cell types. The presence or absence of B cells using flow cytometry is useful as a marker for congenital forms of agammaglobulinemia, which is characterized by absent or extremely decreased circulating B-cell numbers. Characterizing B-cell subsets,

particularly memory and immature B cells, is useful in evaluating patients with CVID. Immunophenotyping for an infant suspected of having SCID will help establish the diagnosis and provide information to help determine the associated genetic defect (Table 18-2).

3. T-cell functional assessment. Delayed hypersensitivity skin tests using *Candida* extract and tetanus antigen have been traditionally used to test functional T-cell responses; however, the results of such testing can be difficult to interpret, and these reagents are no longer commercially available.

More definitive insight into the T-cell functional capability is done by lymphocyte proliferation *in vitro* in response to mitogens and antigens. Mitogens activate cells nonspecifically; approximately 80% or more of peripheral blood T cells will respond. Phytohemagglutinin (PHA) and concanavalin A (Con A) activate T cells predominately, and pokeweed (PWM) mitogens stimulate both T and B cells. Recall antigens, such as tetanus and diphtheria toxoids or *Candida,* stimulate only antigen-specific T cells. After a period of culture (3 days for mitogens and 5 to 7 days for antigens), the extent of cell division is determined either by radioisotope incorporation or other method and compared to healthy control cells. A positive test with mitogens and recall antigens excludes a more severe T-cell defect. Antigen tests are not useful for infants younger than the age of 2 years because appropriate exposure has not yet occurred to allow for recall responses.

4. Polymorphonuclear leukocyte analyses. Aside from persistent or cyclic neutropenia (that must be first excluded), an important polymorphonuclear leukocyte disorder is **chronic granulomatous disease (CGD)**. In the presence of a suggestive history, this diagnosis should be considered on the first clinic visit. The neutrophil oxidative burst pathway for CGD screening is generally assessed with the flow cytometric assay using dihydrorhodamine 1, 2, 3 (DHR); this test has mostly replaced the nitroblue tetrazolium test (NBT) as it is more sensitive and more easily obtained, but the blood must reach the testing laboratory in good condition within 24 hours (see Chapter 20, Diagnostic Immunology, Section IV.B.2). The hyper-IgE syndrome is phenotypically similar to CGD; however, defective polymorpho-nuclear leukocyte (PMN) function is not a clear feature of this disease. The diagnosis is suggested by the identification of IgE levels higher than 2,000 IU/mL (and up to levels of 20,000 to 60,000 IU/mL) with the appropriate clinical manifestations.

5. Assessment of the complement system. The screening test for defects in the **classical complement pathway is the total hemolytic complement activity (CH50) assay**. The **AH50 assay**, not commonly available, is used for defects in the **alternative pathway (see Chapter 20, Section V)**. If the complement screening test results are abnormal or the clinical history suggests a complement deficiency, further studies include measurement of individual complement components (immunochemical and functional assessment may be required). Specific testing for individual complement levels and their split products can be done at specialized centers. Given the lability of the complement proteins, it is important that the serum or plasma obtained for these analyses reach the laboratory in optimum condition for testing; it is

important to check with the clinical laboratory regarding proper sample handling before taking blood from the patient. C3 and C4 levels are often depressed in immune complex–mediated diseases such as systemic lupus erythematosus. Complement testing for hereditary angioedema usually requires measurement of both C1 inhibitor antigenic levels and C1 inhibitor functional levels. In cases of suspected acquired deficiency of C1 inhibitor, levels of C1q should be measured.

C. Advanced Testing

1. Analysis of other cell proteins and receptors. Other cell surface receptors can be examined by flow cytometry and can be essential in the evaluation of PI defects. For example, activation of T cells leads to the expression of CD40 ligand, but this does not occur normally in males with the X-linked form of hyper-IgM syndrome. Intracellular expression of the Wiskott-Aldrich protein, performed in selected centers, aids in distinguishing patients with more profound defects. Leukocyte adhesion deficiency is characterized by defects of the integrin CD18, the common β-chain of LFA-1, Mac-1, and p150, 95 molecules that can be examined also by flow cytometry. The presence or absence of SH2 domain–containing protein 1A (signaling lymphocyte activation molecule [SLAM]–associated protein or SAP) expression detected by flow cytometry provides a useful screening tool to diagnose X-linked lympho-proliferative syndrome (XLP). Flow cytometric analysis for intracellular perforin in cytotoxic lymphocytes has been useful in identification of patients with hemophagocytic lymphohistiocytosis (HLH).

2. Adenosine deaminase and purine nucleoside phosphorylase deficiencies (enzymes related to purine metabolism) are associated with two forms of SCID. Adenosine deaminase (ADA) deficiency is found in approximately 25% of infants, while defects in purine nucleoside phosphorylase (PNP) are very rare. Both enzymes are usually measured in erythrocyte lysates. If blood transfusions have been given within 3 months, the assay for these enzymes may be unreliable, and skin fibro-blasts, grown from a skin biopsy, must be tested instead.

3. Genetic tests. The most commonly used genetic test in the PI diseases is fluorescent in situ hybridization (FISH) for the chromosome 22 abnormality present in DiGeorge's syndrome. This test is designed to determine deletions of the 22q11.2 region of the chromosome in this syndrome. Molecular techniques are essential for the diagnosis of many PI diseases, but tend to be expensive, and best ordered by specialty centers caring for these patients. As the laboratory data and family history for XLA and CGD are sufficient for treatment, genetic confirmation is not important for most patients but may be desired to determine carrier states. For other syndromes, confirmation may be more important, as for SCID, hyper-IgM syndromes, IPEX, and XLP among others.

IV. TREATMENT OF IMMUNODEFICIENCY DISORDERS

A. Antibiotics in acute illness. Antibiotics should be started immediately for fevers and other manifestations of infection after blood and other appropriate cultures have been obtained. These cultures are important to direct further therapy if the infection does not respond to the initial

antibiotic chosen. The choice and dose of antibiotic for a specific infection are usually identical to those used in immunocompetent patients. If the infection does not respond to antibiotics, the possibility of viral, fungal, mycobacterial, or protozoan infection or mycoplasma infections should be considered.

B. Management of specific infections. Chronic otitis media should be treated aggressively in both infants and adults, with antibiotics and with myringotomy tube placement, when indicated. Special attention should be directed to preventing hearing loss, incorporating routine audiologic evaluations into the treatment plan. Sinusitis requires aggressive antibiotic therapy and topical decongestant therapy during acute episodes. If symptoms continue, daily lavage procedures using nasal irrigators with adaptors and saline solutions are useful. If these fail, consider conservative surgical treatment (such as lavage or endoscopic sinus surgery) to drain abscesses as well as to identify the infecting organism(s). Sinus procedures should be avoided unless absolutely needed. Patients with chronic pulmonary disease should be followed with yearly pulmonary function testing including diffusion capacity. Chest radiographs or chest computed tomography (CT) scans should be used sparingly. The importance of a home treatment program of postural drainage and inhalation therapy should be emphasized in patients with respiratory damage such as bronchiectasis.

C. Prophylactic antibiotics can be of benefit in immunodeficiency syndromes and are required in some. Patients with CGD are maintained on lifelong trimethoprim sulfa (TMS) and either itraconazole or voriconazole in treatment doses chronically. Patients with hyper-IgE syndrome are usually treated the same doses of TMS and antifungals, as needed. There is no consensus about the use of prophylactic antibiotics in patients with XLA or CVID, with or without lung disease. Many physicians only treat acute or chronic infections, while others use continuous antibiotic coverage for both, often TMS in treatment or half doses. Others used rotating coverage, including amoxicillin–clavulanate, erythromycin, trimethoprim and sulfa-methoxazole, or a cephalosporin. In adults, amoxicillin–clavulanate, trim-ethoprim and sulfamethoxazole, tetracyclines, or a cephalosporin are useful. Macrolides have been shown to provide substantial anti-inflammatory effects and have been increasingly used. Quinolones with fewer daily doses can also be used but may be best saved to treat acute infections.

D. Strict indications for the use of **corticosteroids** and other **immunosup-pressive agents** should be observed in immunodeficient patients.

E. Immunoglobulin (Ig) replacement therapy is the primary treatment of PI defects in which there is antibody deficiency including XLA, CVID, hyper-IgM syndrome, and combined immunodeficiency disorders, such as SCID and Wiskott-Aldrich. Commercially available intravenous (IV) and subcutaneous (SC) immunoglobulin preparations contain IgG antibodies (with trace amounts of IgA and IgM) in concentrations sufficient to protect against sepsis and to reduce recurrent or chronic pulmonary infections. Products available commercially are listed in Table 18-5. Children diagnosed with transient hypogammaglobulinemia do not generally require replacement Ig. A rare patient with IgA deficiency requires Ig treatment because of significantly reduced antibody production; in these cases (and in some with CVID), Ig products with very low levels of IgA may be required if anti-IgA antibodies are present.

Table 18-5 Current Immunoglobulin Replacement Products (IV and SC)

Brand	Flebogamma DIF	Gammagard S/D	Gammagard Liquid	Gammaplex	Gamunex-C	Hizentra	Octagam	Privigen	Vivaglobin
Manufacturer	Grifols	Baxter	Baxter	Bio Products	Talecris	CSL Behring	Octapharma	CSL Behring	CSL Behring
Dosage Form	5% or 10% liquid	5% or 10% lyophilized	10% liquid	5% liquid	10% liquid	20% liquid	5% liquid	10% liquid	16% liquid
Approved route of administration	IV	IV	IV	IV	IV or SC*	SC	IV	IV	SC
IgA content	<50 µg/mL in 5%; <100 µg/mL in 10%	<2.2 µg/mL	37 µg/mL	<10 µg/mL	46 µg/mL	≤50 µg/mL	<100 µg/mL	<25 µg/mL	≤ 1,700 µg/mL
IgG (%)	≥97	≥90	≥98	≥95	≥98	≥98	>96	≥98	≥96
Sodium content	<3.2 mmol/L	8.5 mg/mL in 5%; 17 mg/mL in 10%	No added sodium	30–50 mmol/L	Trace	Trace (≤10 mmol/L)	≤30 mmol/L	Trace	3 mg/mL
Sugar content	50 mg/mL D-sorbitol	20 mg/mL glucose in 5% solution; 40 µg/mL in 10%	No added sugar	5% D-sorbitol	None	None	100 mg/mL maltose	No added sugar	None
pH	5.0–6.0	6.4–7.2	4.6–5.1	4.8–5.1	4.0–4.5	4.6–5.2	5.1–6.0	4.8	6.4–7.2

*Gamunex-C can be administered intravenously or subcutaneously for primary immunodeficiency. Subcutaneous use is not indicated for idiopathic chronic inflammatory demyelinating polyneuropathy.

IV, Intravenous; SC, subcutaneous

1. **Route of Administration.** Both intravenous and subcutaneously delivered Ig are safe and effective replacement strategies; convenience to the patient guides this choice. Some advantages of the IV route include achieving rapid increases in plasma levels, a monthly interval of treatment, and reduced bruising in those with coagulation disorders. IVIg may be administered in the doctor's office, infusion center, or home; if at home, IVIg may be self-administered or by an infusion nurse. Indwelling ports are discouraged as they are a frequent source of infection, may lead to thrombosis, and eventually need replacement. Poor intravenous access can be addressed by the use of SC gammaglobulin. Subcutaneous infusions may be given in a number of ways, most commonly by a small portable syringe driver or pump with a 10- to 20-mL syringe and infusion set with a 25- to 27-gauge SC needle. The subcutaneous route is helpful in patients who experience rate-related side effects (including, but not limited to, myalgias, fatigue, low-grade fevers, chills, nausea), have increased metabolism of Ig products, or prefer the convenience of this form of self-administration. Because smaller amounts are given more frequently, patients on SCIg achieve a more stable serum level of IgG, eliminating the need for assessing trough levels.
2. **Dosage.** There are a number of commercially available Ig preparations (Table 18-5). Each is well tolerated and effective at restoring IgG antibody. The usual starting dose of IVIg is approximately 400 to 600 mg/kg, given every 3 or 4 weeks. Typically, the first dose of IVIg is divided in half, and the dose is repeated 2 weeks later to achieve a full dose, after which subsequent treatments are given every 3 to 4 weeks. Trough serum IgG levels 4 weeks after treatment should be maintained >600 mg/dL (approximating low normal levels). Consistent trough levels are usually achieved after 3 to 6 months of therapy. For SC treatment, the required monthly dose is usually divided into biweekly or weekly doses after converting into milliliters based on the concentration of the product, usually 100 to 150 mg/kg/week. Generally, adult patients tolerate 15 to 20 mL per infusion site, depending on the amount of subcutaneous tissue (usually given in the abdominal wall

or lateral thigh). Other methods include giving much smaller doses by slow SC push, daily or every other day, which avoids the use of the pump.

Whichever route is chosen, particular attention must be given to patients with chronic lung or gastrointestinal disease or previous autoimmunity to ensure that adequate trough levels are maintained. Some studies report that dosages up to 600 mg/kg/month and trough levels >800 mg/dL may better control chronic pulmonary infections and improve pulmonary functions when compared with lower dosages. Individualization of the dosage and dosing frequency is based on clinical response and determination of trough serum IgG levels, as variability in the metabolism could influence efficacy of therapy. Serial immunoglobulin assays are generally not necessary to gauge the effectiveness of treatment, although many immunologists test serum IgG levels at 4- to 6-month intervals to ensure maintenance of adequate trough levels; once on stable doses, their trough can be measured at 6- to 12-month intervals. During acute infections, gamma globulin metabolism increases, and higher dosages or shorter intervals of infusions may be required.

3. **Adverse effects.** Initial administration of IVIg should be under supervision of experienced personnel. The majority of reactions are minor and transient. Fever, chills, nausea, vomiting, and back pain can occur with IVIg, especially during or after the first several infusions. These are often related to the rate of infusion or underlying, concomitant host infection. More severe reactions, such as anaphylactic reactions (hypotension, flushing, or bronchospasm), are very unusual but can occur. These adverse reactions can be caused by aggregated IgG or, much more rarely, anti-IgA antibodies. Some individuals have reactions when IVIg products are switched from one brand to another. Severe systemic reactions require immediate treatment. For subsequent IVIg administration in patients with severe reactions, the following measures should be taken:

   a. Reassess the need for intravenous immunoglobulin G. Is the patient truly IgG deficient, and will he or she benefit from IVIg administration?

   b. Rate-related reactions in new patients or patients receiving a new product can be resolved by slowing the initial infusion or by gradual stepwise increase.

   c. Determine if the brand of intravenous IgG has been changed, and return to a better-tolerated product.

   d. Test for anti-IgG antibodies to IgA (at commercial laboratories or the American Red Cross). Although IgE anti-IgA antibodies can cause anaphylactic reactions, individuals who have IgE anti-IgA appear to also have IgG anti-IgA, so these patients at risk can be identified. If the reaction is due to anti-IgA antibodies, IVIg products depleted of IgA (Table 18-5) can be used. The first infusions in such a circumstance should be done in a controlled setting, starting with a small dose. Patients with anti-IgA antibodies may also better tolerate the SC route.

   e. Consider pretreatment. Some practitioners pretreat with diphen-hydramine (Benadryl), acetaminophen, and/or corticosteroids before infusions. Although effective in preventing severe reactions in some patients, pretreatment can also mask early systemic manifestations.

   f. Splenectomy is a relative contraindication, as severe infections have occurred; only

under the most severe and unusual circumstances, such as to control bleeding in treatment failure and uncontrolled autoimmune cytopenias, extreme hypersplenism, or lymphoma, is splenectomy warranted. The addition of the phagocytic defect (i.e., as a result of splenectomy) to an already existing immunologic defect can significantly increase the risk of sudden, overwhelming sepsis. Similarly, tonsillectomy and adenoidectomy should be performed only rarely and with strictly narrow indications.

V. SPECIFIC TREATMENT FOR CELLULAR DEFICIENCY

Specific treatment for T-cell immune deficiencies is complicated because these disorders often involve heterogeneous defects; some are very severe, whereas others are milder. This heterogeneity makes it difficult to determine the exact requirements for complete immunologic reconstitution. As a result, a number of treatment approaches are currently employed; however, because of the complexity of diagnosis and treatment, such patients are usually cared for by referral centers with an investigative capacity and interest in the specific PI disease.

A. Bone marrow/stem cell transplantation. Bone marrow, mobilized stem cells, and placental blood contain postthymic T cells and pluripotent stem cells that can differentiate into the hematopoietic, lymphoid, phagocytic, and megakaryocytic cell series. Bone marrow, peripheral blood, and placental stem cells, providing precursors for a variety of cell systems, have been used successfully in most PI diseases, and early referral to a specialist is important. Extensive medical support is required to care for severely immunocompromised patients before and after transplantation. Outcome after transplantation for these diseases is dependent on the age of diagnosis and intervention, type of donor match, and history of infections. Complications include infection, graft rejection, GVHD, and posttransplant lymphoproliferative disease. Transplantation for PI defects should be done only in medical centers equipped to provide the needed clinical services.

B. Enzyme replacement. The autosomal recessive form of SCID ADA deficiency can be treated by enzyme therapy using bovine ADA, modified by conjugation with polyethylene glycol (PEG-ADA). This allows for markedly increased amounts of plasma ADA, resulting in significant clinical improvement accompanied by varying degrees of immunologic improvement.

C. Gene therapy. Increasingly explored for PI defects, two forms of SCID, X-linked and ADA deficiency, can be successfully treated with gene therapy. Other recent successes include Wiskott-Aldrich syndrome, CGD, hyper-IgM syndrome, XLP, and IPEX syndrome. This work is rapidly advancing, but there remains concern for insertional oncogenesis with potential for lymphoproliferative disease.

D. Cytokines. Cytokine therapies provide benefit in patients with PI defects as well, but these are in selected instances. G-CSF is commonly used for patients with severe congenital neutropenia who can respond to this therapy and intermittently or continuously to patients with cyclic neutropenia. Interferon-gamma (IFN-γ) is often used in CGD to reduce the frequency and severity of infections. Some patients with SCID and CVID demonstrate enhanced T-cell function when treated with low doses of interleukin 2 (IL-2). IL-2, when administered to patients with idiopathic CD4+ lymphopenia, can result in an increase in CD4+ T-cell counts. Interferon-alfa (IFN-α) has shown activity in Epstein-Barr virus (EBV)–induced B-cell lymphomas in patients with X-linked lymphoproliferative syndrome (XLP). IFN-α has been used by some practitioners

to treat molluscum contagiosum in patients with hyper-IgE syndrome and CD4+ lymphopenia.

VI. SPECIFIC TREATMENT FOR COMPLEMENT DEFICIENCY

Definitive treatment for complement deficiency requires replacement of the specific missing protein. The only currently available complement component for replacement therapy is for C1 inhibitor deficiency. The goal of treatment is to eradicate infections, particularly encapsulated organisms, and control of autoimmune conditions with anti-inflammatory therapy. In patients with recurrent infection, treatment with prophylactic antibiotics can be considered. All patients with complement deficiency should receive routine vaccinations including those for meningococcal and pneumococcal since they are at increased risk. **Fresh frozen plasma** from normal donors can replace specific complement components in patients with isolated complement component defects. The risks of exposure to or infection by a wide range of blood-borne pathogens make this therapy impractical on a long-term basis; moreover, it can lead to development of autoantibodies.

VII. GENERAL CONSIDERATIONS

A. Diet. No special dietary limitations are necessary except in patients with malabsorption and diarrhea. In these patients, professional dietary consultation is helpful to ensure that the diet is adequate in calories, protein, trace elements, and vitamins for normal growth and development. Chronic malnutrition can further depress a variety of immune functions.

B. Avoidance of pathogens. Patients with immunodeficiencies, especially if T-cell functions are impaired, should be protected from unnecessary exposure to infection. Limiting exposure to other young family members and isolation from persons with respiratory or other infections, especially herpes simplex and varicella-zoster, are important. Patients with antibody deficiency can have a normal life span with replacement Ig therapy, should not be isolated from others, and should be encouraged to participate in all usual activities. An affected child should similarly be encouraged to go outdoors, to play with other children in small groups, and to attend nursery school and regular school. Special avoidance measures are necessary for patients of any age who have CGD due to a marked susceptibility to certain fungi, such as *Aspergillus*, found in moldy vegetation (hay, grass clippings, raked leaves). Drinking water from private wells or public sources that do not use a filtration system may be contaminated with cryptosporidium, which poses additional risk to patients with hyper-IgM.

C. Whole-blood transfusions should be avoided in patients who have or are suspected of having a cellular immunodeficiency because infused donor lymphocytes can cause a fatal graft-versus-host reaction. If any transfusion is necessary, the blood product should be irradiated before administration. In addition, cytomegalovirus-free blood products should be used in patients who are immunodeficient or have posttransplantation status.

D. Administration of live virus vaccines (e.g., poliovirus, rotavirus, yellow fever, varicella, live influenza, measles, mumps, rubella, and BCG) is to be avoided in all immunodeficient patients, especially in those with a cellular immunodeficiency. These vaccines carry the risk of vaccine-induced infection; in years past, when smallpox vaccine was being routinely administered, parents, siblings, and other household members were not vaccinated because of the high risk of spreading the infection to the patient. Patients treated with immunoglobulin are partially

protected from these diseases through passive transfer of antibodies contained in the infusions. Vaccines using inactivated organisms are generally regarded as safe, and their use for stimulating a measurable antibody response can be of diagnostic value.

E. Psychosocial support. Because of the severe psychological and financial demands placed on severely affected patients and their families, attention must be paid to these aspects of their lives. The school age–children administrators should be made aware of the problems and work to provide tutors to help make up for school absences. Financial counselors can give the patient or the family information about agencies that provide partial or complete financial support for medical care. Agencies for crippled children in many states can provide help for immunodeficient patients.

Both the **Immune Deficiency Foundation** (40 W. Chesapeake Avenue, Suite 308, Towson, MD, 21204; phone: 410-321-6647 and 800-296-4433; fax: 410-321-9165; www.primaryimmune.org) and the **Jeffrey Modell Foundation** (phone: 866-INFO-4-PI; 212-819-0200; fax: 212-764-4180; www.jmfworld.com) provide educational information to patients and parents, support scientific meetings, and offer additional support services including information about insurance reimbursement. Regional patient retreats and conferences offered by such foundations provide opportunities for patients and their family members to meet other families and physician experts in the field of immunodeficiency. The **International Patient Organization** (www.ipopi.org) is an international group with an interactive website giving information about news and publications in primary immunodeficiency diseases, bulletin boards, and a chat room. The **National Organization of Rare Diseases** (NORD Inc., 55 Kenosia Avenue, P.O. Box 1968, Danbury, CT 06813; phone: 203-744-0100; www.rarediseases.%20org) is another organization that has been an additional resource for support.

The **United States Immunodeficiency Network** (USIDNET, 40 W. Chesapeake Avenue, Suite 308 Towson, MD 21204; phone 866-939-7568; www.usidnet.org) was established to advance scientific research in the primary immune deficiency diseases. USIDNET maintains a registry of patients with primary immunodeficiency diseases to provide an estimate of the prevalence of each disorder in the United States. They also maintain a cell/DNA repository of biologic material from patients with well-characterized immunodeficiencies for the advancement of scientific research.

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19

Approach to the Patient with Recurrent Infections

Zuhair K. Ballas

INTRODUCTION

The environment is rife with multiple microorganisms. In addition to the microorganisms that surround us, microorganisms are an integral part of our biologic makeup. It is estimated that the microorganisms in a human outnumber the body cells by up to 10:1. Thus, for example, the skin supports a high density of microorganisms, the sinonasal tissue and the oral cavity are host to multitudes of organisms, and the colon is estimated to have as much as 10^{10} organisms per gram of tissue. It is therefore not surprising that humans get infected as much as it is surprising that normal subjects rarely get infected

I. PHYSICAL BARRIERS

While immune mechanisms are integral in the defense against infections, nonspecific defenses play an equally important role in the defense against infections. Thus, an intact skin is an essential part of the defense against infection, and it is well established that it takes very few bacteria to infect a wound compared to a multitude that is needed to infect an intact skin. The skin defends against infection not just by being a physical barrier but by the local production of fatty acids that have potent antimicrobial activity. Mucosal surfaces also have several molecules that are produced locally, such as defensins, which have antimicrobial activity. Other nonspecific local defenses include cilia, which act as a "mop" to sweep away microbes, and mucus, which serves as a "rinsing" agent. The importance of an optimal production and viscosity of mucus is best illustrated by cystic fibrosis where excessively viscous mucus is not efficient at cleaning mucosal surfaces. Acidic pH in the stomach acts as a potent antimicrobial agent; it is not unusual to hear of cases where the same load of bacteria may or may not produce food poisoning depending on whether it was consumed on an empty (acidic) or full (neutral or basic pH) stomach. Indeed, it has been known for some time that gastrectomy is associated with an increased incidence of mycobacterial infection. It is therefore important that the status of the various barriers be examined first in any patient with a history suggestive of recurrent infections especially if such infections are limited to one organ system.

II. COMORBIDITIES

Secondary immunodeficiencies leading to recurrent infections are much more common than primary immunodeficiencies. Worldwide, malnutrition is probably the most common cause of recurrent infections. In North America, primary malnutrition may not be as common, but

malnutrition in the "older old" (those over 75 years of age) is becoming, and will continue to become, a common occurrence.

Other common causes of secondary immunodeficiency include:

- HIV
- Malignancy
- Metabolic diseases (diabetes, severe liver disease, chronic kidney disease)
- Immunosuppressive drugs (chemotherapy or antigraft rejection drugs in the setting of organ transplantation)
- Immunomodulatory agents (e.g., TNF antagonists, rituximab, abatacept)
- Drug-induced hypogammaglobulinemia (especially antiepileptics such as diphenylhydantoin, carbamazepine, valproate)
- Protein loss through the GI tract or through the kidneys or secondary to severe burns

III. RECOGNITION OF VARIOUS MICROORGANISMS

The tug-of-war between host and pathogen has been going on for millennia. The phylogeny of primitive, nonspecific, or "innate" immune defenses predates the advent of antigen-specific immune responses. Nevertheless, innate immune mechanisms persist in humans and are the first line of defense against most microorganisms. Innate immunity has "sensors" which recognize molecular patterns rather than specific antigens as is the case with adaptive immunity. Redundancy is a well-known characteristic of adaptive immune responses, but redundancy is also prevalent in innate immunity in that a given molecular pattern may be recognized by more than one nonspecific innate immune "sensor." A classically recognized innate immune "sensor" is mannose-binding protein on the surface of neutrophils and macrophages, which binds to mannose on the surface of gram-negative bacteria and some fungi. Another well-known innate sensor is the mannan-binding lectin pathway of the complement system. Several other innate "sensors" have been recognized recently, and they belong to distinct "families" (with more to be characterized):

- Toll-like receptors (TLR)
- C-type lectin receptors (CLRs)
- Nucleotide-oligomerization domain (NOD) proteins
- NOD-like receptors (NLR)
- Retinoic acid-inducible gene I(RIG-I)-like receptors (RLR)

Binding to these pattern recognition receptors activates signal transduction pathways that result in the activation of cytoplasmic and nuclear factors that ultimately result in the transcription, translation and secretion of various inflammatory mediators, cytokines, and chemokines, and the generation of reactive oxygen species and various antimicrobial effectors. To date, TLR are the most extensively studied pattern recognition receptors. For example, endotoxin is expressed on

gram-negative bacteria and is recognized by TLR4. Lipoteichoic acid is expressed on some gram-positive bacteria and is recognized by TLR2. A simplified pattern of recognition by the various TLR is shown in Table 19-1.

Table 19-1 TLR and Their Recognition Pattern

• TLR1 and TLR2:	Mycobacteria
• TLR3:	Double-stranded RNA
• TLR4:	Endotoxin/Lipid A
• TLR5:	Flagellin
• TLR6:	Mycoplasma
• TLR7 and TLR8:	Single-stranded RNA
• TLR9:	CpG DNA
• TLR10:	Unknown
• TLR11:	Uropathogenic bacteria
• TLR12 and TLR13:	Unknown

The function of innate sensors is to facilitate phagocytosis and intracellular killing by the elaboration of intracellular antimicrobial mechanisms. This process is probably of most importance in defense against pathogens that enter through mucosal surfaces. In addition to phagocytes, NK and NKT cells are part of the innate immune systems and are thought to be the major and earliest producers of interferon and IL4 which in turn activate the adaptive immune system.

Other locally important mechanisms aimed at limiting pathogen invasion and spread include the coagulation pathway and the elaboration of vasoactive molecules leading to vasoconstriction.

One of the mechanisms by which ingested organisms are destroyed is the generation of reactive oxygen species (ROS) by macrophages or neutrophils. Some organisms produce catalase which inactivates ROS. Therefore, if the host's oxidative pathway is suboptimal (as occurs in chronic granulomatous disease), there will be an increased incidence of infection by catalase-producing organisms such as *Candida*, *Aspergillus fumigatus*, *Staphylococcus aureus*, *Klebsiella*, *Serratia*, *and Pseudomonas*.

In the tug-of-war between microorganisms and host defenses, some bacteria evolved a "capsule." Encapsulated bacteria use their polysaccharide capsules to hide some of their surface molecules. In response, the host adopted a new defense strategy aimed at recognition of the capsular polysaccharide with the same ultimate goal of promoting phagocytosis. This recognition is mediated by antibodies generated to recognize the capsule. The antibody–antigen complex will activate complement thus facilitating opsonization and the ingestion of the encapsulated bacteria. For reasons not entirely clear, the terminal complement components are important in defense against *Neisseria* species.

The primary strategy in the defense against gram-negative and encapsulated bacteria is to facilitate phagocytosis since once ingested, these organisms are readily digested. However, some organisms, such as mycobacteria, are resistant to intracellular digestion by resting macrophages. The strategy for such organisms is to activate the macrophages by marshaling T-cell responses, CD4 T cells in particular, which secrete cytokines such as interferon gamma (IFNγ). Once activated, macrophages are able to neutralize most intracellular organisms.

For viruses, a different strategy was needed since they do not usually infect professional phagocytes, so the macrophage activation approach is not feasible. For such organisms, the development of cytotoxic T lymphocytes (which can be CD4 but usually are CD8) was needed.

It is therefore apparent that the type of organisms seen in a patient with recurrent infections should give an indication as to which arm of the immune system is likely to be dysfunctional (Table 19-2).

Table 19-2 The Infections May Indicate the Deficiency

Infecting Organism	Dominant Immune Defense
Gram-negative bacteria	Neutrophils
Encapsulated bacteria	Antibody response or early complement components
Neisseria	Terminal complement components
Intracellular	T lymphocytes, NK cells
Catalase producing	Phagocytes

The above scheme applies for most of the commonly encountered immunodeficiencies. Recent advances, however, suggest that the immune system is far more sophisticated in that there may be a dominant pathway for each particular microorganism although this remains somewhat of a broad generalization. Nevertheless, due to our still limited understanding of the various immune pathways, it is often difficult to predict the outcome of a selective inactiva-tion or overexpression of a single cell, cytokine or molecule. This point has been established by the infection patterns in several mutant mice as well as by selective abnormalities that have been described in humans. For example, patients with mutations in their Interferon-gamma (IFNg) or IFNg-receptor (IFNR) display selectively increased susceptibility to infections with mycobacteria. Patients with IL-12 mutations have a selectively increased susceptibility to infections with atypical mycobacteria or salmonella. Certain polymorphisms in TLR molecules have been associated with infections dominated by one or two microorganisms (examples are shown in Table 19-3).

Table 19-3 Specific Infections Associated With TLR Mutations

TLR Polymorphism	Dominant Infection
TLR2	Mycobacteria, *S. Aureus*
TLR3	HSV encephalitis
TLR4	Gram-negative sepsis, *Neisseria*, RSV, invasive aspergillosis
TLR5	*Legionella*

IV. WHICH INFECTIONS SHOULD RAISE SUSPICION?

Recurrent and frequent infections are the primary clinical picture which prompts most physicians to wonder about immunodeficiency. In determining what constitutes an abnormal frequency of infections, one should take the patient's environment into consideration. For example, recurrent URI's in a child going to daycare are probably due to increased exposure rather than suboptimal defenses. Recurrent "bronchitis" in a heavy smoker most likely indicates organ damage rather than abnormal host defenses. Detailed and documented history of the infections is probably the most useful tool for such patients. One needs to seek documentation of the infection by either culture or imaging when appropriate. Allergic rhinitis may be frequently misdiagnosed as recurrent sinusitis. Asthma may be misdiagnosed as recurrent pneumonias. A history that such

recurrent episodes respond to antibiotics is not in itself indicative of bacterial infections since many viral infections are self-limited and were probably going to resolve on their own by the time antibiotics were dispensed. Recurrent bacteremia in a patient with an indwelling catheter is a serious and life-threatening infection but is most likely due to colonization of the catheter.

For a child, two or more serious sinus infections or pneumonias in 1 year are considered excessive as would be two or more episodes of sepsis or meningitis. In general, for children the following history is considered suggestive of an underlying immune abnormality:

- <8 ear infections per year
- <2 months of antibiotics per year
- Recurrent oral thrush
- Need to receive IV antibiotics
- Recurrent skin abscesses
- Opportunistic infections

For an otherwise healthy nonsmoking adult, three documented sinus episodes a year would be considered excessive as would be one episode of documented pneumonia per year even though some suggest that one episode of pneumonia every 5 years might also be considered excessive.

In thinking about other aspects of infections that should raise a flag, one should think of the **"unusual" rule**:

- Unusual frequency
- Unusual duration
- Unusual severity
- Unusual complications
- Unusual organisms

For example, a community-acquired pneumonia that results in empyema or results in the patient being placed on a ventilator should raise one's index of suspicion. A documented pneumonia that does not resolve despite adequate antibiotic therapy is not "normal." Infection with opportunistic organisms or organisms of low virulence (such as atypical mycobacteria) is also abnormal. Bacteremia or brain abscesses with no apparent entry point should warrant a further look at the immune system.

On the other hand, recurrent infections in the same anatomical site may indicate local abnormalities rather than abnormal host defense. For example, recurrent pneumonia documented by x-ray but always in the same region may indicate local abnormalities such as obstruction or bronchiectasis. A patient with multiple skin grafts due to severe burns in an extremity might have poor blood supply and hence might have an increased susceptibility to infection at that site. In addition to the history of infections, the patient's overall well-being needs to be taken into consideration. Failure to thrive is a well-known indicator for possible immunodeficiencies in children. Hence, a child who is failing to thrive needs to be investigated

even if he or she goes to day care or has only one or two overt infections a year. Similarly, adults also show symptoms of failing to thrive although not as dramatically as children. For adults, frequent hospitalizations (two to three times a year) and unexplained cachexia or muscle wasting may be the earliest signs of an underlying immune abnormality.

V. NONINFECTIOUS CLUES

Although infections are the most common presentation of immunodeficiency, they are not the only consequence. Indeed, even patients with documented hypogammaglobulinemia may not have infections as their presenting symptoms. Noninfectious conditions that should raise a flag as to an abnormal immune system are shown in Table 19-4.

Table 19-4 Nonclassical Clues for Immunodeficiency

- Poor wound healing
- Complications from a live vaccine
- Dentures at an early age
- Recurrent gingivitis
- Recalcitrant warts
- Frequent and persistent aphthous ulcers
- Multiple autoimmune diseases
- Recurrent mucosal or oral candidiasis
- Chronic diarrhea or malabsorption
- Unexplained bronchiectasis
- Failure to thrive
- Family history of immunodeficiency
- Consanguinity (raises possibility of recessive genetic diseases)

VI. PHYSICAL EXAMINATION

Physical examination may give valuable clues about underlying disease processes. In children, certain features might suggest syndromic disease. For example, the presence of wide-set eyes, fish-mouth, and low-set ears might indicate DiGeorge's syndrome. Lymphadenopathy may indicate an abnormality of apoptosis, an infection, or a malignancy. Suppurative adenitis might indicate CGD. Evidence of active or healed abscesses limited to the axillae and groins should suggest the diagnosis of hidradenitis suppurative. Lack of tonsil tissues may indicate X-linked agammaglobulinemia or SCID. Growth and development by growth charts and maturational milestones in children should be examined. Cachexia or muscle wasting in adults should be checked as well. Examination of the skin might offer clues as to atopic dermatitis which is associated with several immunodeficiency disorders. Petechiae might indicate thrombocytopenia, and palpable purpura might indicate vasculitis. Skin might reveal furuncles, abscesses, telangiectasia, or warts. Scars need to be examined as they may give a clue of poor wound healing as well as the location of previous surgery (such as splenectomy). Nail examination might indicate infection (onychomycosis), psoriasis (pitting), thyroid disease (onycholysis), systemic disease (splinter hemorrhages or dilated capillary bed), or lung disease (clubbing or yellow nail syndrome).

The presence of acute or chronic otitis media with or without hearing loss is an important finding

in children; perforated tympanic membranes and purulent drainage might indicate immune abnormalities. In general, the presence of drainage tubes in the ears of an adult is a very strong indicator of a suboptimal immune system

The presence of nasal polyps might indicate cystic fibrosis or (in association with asthma) might indicate Samter's triad of nasal polyps, asthma, and aspirin sensitivity. Nasal polyps in a patient with history of recurrent sinus "infections" might indicate the possibility of allergic fungal sinusitis or noninfectious hyperplastic eosinophilic sinusitis. Purulent looking secretions are not sine qua non with infection as eosinophilia can also look purulent.

Oral exam should look for aphthous ulcers, gingivitis, oral candidiasis, poor dentition, posterior pharyngeal lymphoid hyperplasia, tonsil size, and postnasal drip.

Neck exam should look for thyroid abnormalities, enlarged salivary glands (sialadenitis is a common finding in some immunodeficiencies), and enlarged lymph nodes, and lung exam might indicate obstructive airway disease, consolidation, or localized disease. Cardiac exam might indicate the possibility of congenital heart disease that is associated with chromosome 22q deletion. Hepatosplenomegaly might indicate an underlying disease. Musculoskeletal exam might give evidence of inflammatory joint disease, spondyloepiphyseal dysplasia (seen in cartilage hair syndrome), muscle wasting, temporal tenderness (giant cell arteritis), or proximal muscle weakness (polymyositis). Neurologic exam should look for any focal deficits as well as neuropathy (pernicious anemia is seen with a higher frequency in some immunodeficiencies).

VII. WORKUP OF SUSPECTED IMMUNODEFICIENCY

A. Initial screening needs to include CBC with differential looking for

- Leukocytosis (infection, leukemia)
- Neutropenia (immunodeficiency, medications)
- Neutrophilia (infections or leukocyte adhesion deficiency)
- Lymphopenia (immunodeficiency, HIV, malignancy, steroids)
- Eosinophilia (hyper IgE, atopy, lymphoma, parasitic infestations, Wis-kott-Aldrich syndrome, some malignancies)
- Anemia (chronic disease, autoimmune hemolysis)
- Thrombocytopenia (Wiskott–Aldrich, autoimmunity)

B. Other initial tests should include

- Sedimentation rate (ESR) and C-reactive protein as markers of acute inflammation
- Liver function tests including total serum protein, albumin, and globulin
- Urinalysis looking for proteinuria
- HIV (preferably by PCR)
- Imaging should be targeted as suggested by history and physical exam
  - Chest x-ray looking for a thymus shadow if DiGeorge is suspected

- Sinus CT scan for a history of recurrent sinusitis
- High-resolution chest CT scan if bronchiectasis is suspected

• Patients with recurrent skin infections should have nasal cultures looking for carrier status (*S. aureus* being most common).

C. The **second tier of testing** should be dictated by the dominant type of microorganism that has been determined by history and cultures. Infections with catalase-producing organisms should prompt the possibility of CGD. The golden standard is the determination of respiratory burst generation by flow cytometry utilizing the dye dihydrorhodamine (DHR). DHR testing has replaced nitroblue tetrazolium (NBT) as the golden standard test for CGD.

Infections with encapsulated bacteria should prompt measuring immuno-globulin levels including IgG, IgA, IgM, and IgE. For children, one has to ensure that age-matched normal ranges are supplied by the testing laboratory. IgG subclasses are not indicated for screening. Commonly encountered find-ings might include the following examples:

• Agammaglobulinemia (nondetectable IgG, IgA, or IgM) in a male child suggests X-linked agammaglobulinemia (Bruton's disease).

• Nondetectable IgA in the presence of normal IgG and IgM suggests selective IgA deficiency.

• Normal or high IgM with nondetectable IgA or IgG might indicate any of the known hyper-IgM syndromes (in a child), multiple myeloma, or Walden-ström's macroglobulinemia in an adult.

• An elevated IgE suggests atopy or hyper-IgE syndrome.

• Low IgG (less than two standard deviations below normal) along with a similarly decreased IgA or IgM suggests common variable immunodeficiency.

• Low IgG with normal IgA and IgM suggests protein loss (protein losing enteropathy or proteinuria).

• Normal or increased IgG with markedly decreased IgA and IgM might suggest multiple myeloma or a common variable immunodeficiency patient on immunoglobulin replacement.

• Total hemolytic complement (CH50) rules out early complement component deficiencies, which may present with recurrent infection with encapsulated bacteria. It would also rule out terminal complement component deficiencies in a person with recurrent *Neisseria* infections.

• Deficient mannose binding protein can be checked in patients with recurrent gram-negative infections.

• Functional antibody assessment can be determined by measuring specific antibody titers to recently obtained vaccines in children. If the titers are low, then obtaining pre- and postvaccination titers should determine the ability of that person to mount a significant antibody response at that point in time. A "normal" random antipolysaccharide antibody titer in an adult suggests that this person was able to mount an antibody response at some point and that the memory B cells specific for that antigen are persistent. This, however, does not indicate that

this person is able to mount a significant antibody response at the present point in time against new antigens. This is best illustrated by HIV patients who are able to mount an antibody response initially but that ability declines as the CD4 counts decline. Markedly elevated preimmunization antibody titers, however, make it almost impossible to interpret antipolysaccharide antibody responses.

Infections with viruses or intracellular microorganisms should prompt quantitative and qualitative evaluation of cell-mediated immunity. Quantitative analysis relies on enumeration of various lymphocyte subsets by flow cytometry with particular emphasis on measuring the following subsets (for screening purposes):

• T cells (as determined by expression of CD3)

• T cell subsets: CD4 and CD8

• B cells (as determined by expression of CD19 or CD20). Absence of B cells suggests hereditary agammaglobulinemia

• NK cells (as determined by CD3-$CD56^+$ markers)

• Expression of CD11/CD18 and CD15a if leukocyte adhesion deficiency is suggested by history

In addition to the numbers, functional assessment of lymphocyte responses should be undertaken. This is usually done *in vitro* by examining the ability of lymphocytes to respond to antigens, mitogens, anti-CD3, and alloantigen. Phytohemagglutinin and concanavalin A are T-cell mitogens; pokeweed mito-gen is a T-dependent B cell stimulator. Anti-CD3 is probably the most physiologic T-cell stimulus as it approximates stimulation through the T-cell receptor. The T-cell receptor is polymorphic, but it is coupled to CD3 chains that are nonpolymorphic; thus, anti-CD3 stimulation is as close as one can get to TCR stimulation for screening purposes. Response to antigens such as tetanus or candida (to which the patient was previously exposed) serves to determine whether the patient's lymphocytes are able to mount a specific immune response. Response to alloantigen (mixed lymphocyte culture or mixed lymphocyte response) tests the ability of naive T cells to mount a response to new antigens.

Delayed type hypersensitivity (DTH) skin tests, if done and interpreted properly, are quite useful in obtaining a gross assessment of the *in vivo* function of several, but not all, aspects of T-cell–mediated responses. Unfortunately, there is no one antigen to which 100% of the population would be positive. Hence, an ideal DTH battery should include several antigens (5 to 10) before one can conclude with certainty that a patient is anergic. Children <2 years of age may have a negative DTH in spite of an intact cellular immunity. Moreover, a positive DTH indicates the presence of functional CD4 memory cells but gives no information on CD8 cells, naïve CD4 cells, or NK cells.

DTH testing should be undertaken only by somebody who has extensive experience in selecting and applying the antigens proven to be useful in their particular geographic area. Although measurement of the DTH response sounds simple, there have been studies showing a wide interobserver variability in accurately measuring the induration. Common antigens used in DTH include *Candida*, tetanus, recombinant streptokinase, trichophytin,

Histoplasma (in endemic areas), and coccidioidin (in endemic areas). Most physicians are tuned to interpreting PPD skin tests as being positive when the induration is >10 mm. For DTH purposes, a 5-mm induration is considered an adequate response. However, timing of the measurement is pivotal. Early (<24 hours) induration might indicate an Arthus reaction (most commonly seen with tetanus especially if a high concentration is used). A delayed reading (>48 hours) might render a borderline positive (5 to 6 mm induration) as a negative (<5 mm induration). Since activation of the coagulation cascade is part of the induration seen in a positive DTH, patients on anticoagulants might have a false-negative reading.

VIII. SUMMARY

One should develop a high index of suspicion for immunodeficiency especially in adults who may have attenuated phenotypes as opposed to the dramatic course of pediatric patients with SCID or agammaglobulinemia (see Primary Immunodeficiency Diseases, Chapter 18). Nevertheless, the majority of immunodeficiencies in both children and adults are secondary rather than primary. Infections that should prompt consideration for an immune workup should focus on the "unusual" aspects: unusual frequency, unusual severity, unusual complications, unusual duration, or unusual organisms.

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20

Diagnostic Immunology

Thomas A. Fleisher, Joao Bosco Oliveira, and Jack J. H. Bleesing

INTRODUCTION

Techniques for evaluation of immunologic function have expanded dramatically in recent years as understanding of the immune system increases. These studies are useful for the evaluation of patients with suspected immune deficiency disorders and autoimmune, allergic, or malignant diseases. The chapter is directed at general concepts and appropriate applications of methods used to characterize and quantify immuno-globulins and specific antibodies; evaluate lymphocyte phenotype and function; study neutrophil function, assay complement, as well as molecular methods used to enhance these other studies and make a definitive genetic diagnosis.

I. QUALITATIVE AND QUANTITATIVE MEASUREMENT OF IMMUNOGLOBULINS AND SPECIFIC ANTIBODIES

Immunoglobulins are glycoproteins secreted by differentiated B lymphocytes (plasma cells). Specific immunoglobulins (antibodies) are normally produced following antigenic stimulation, yielding a variety of antibody molecules, all of which react with varying strengths to the specific antigen. This type of response is referred to as polyclonal because it involves multiple B-cell clones. The basic molecular structure of the immunoglobulin consists of two identical heavy chains (α, δ, ε, γ, or μ) and two identical light chains (κ or λ) that together form a monomer (see Chapter 1). There are five different classes or isotypes of immu-noglobulin that are determined by the heavy chain used in the molecule (e.g., immunoglobulin G [IgG] contains two identical γ heavy chains paired with two identical κ or λ chains). The Fab portion of the molecule provides the antigen-combining sites, and the Fc portion contains the other sites of biologic function, such as complement component binding. IgG, the most prevalent immu-noglobulin in serum, is found as a monomer and constitutes the major antibody class produced in secondary antibody responses. Both IgE, the antibody of the allergic response, and IgD, a principal B-cell surface immunoglobulin, are also present in serum as monomers but are found in very low concentrations. IgA is found in serum and secretions as a dimer, together with a J chain and secretory component. The secretory component is synthesized by mucosal epithelial cells and joined to the dimeric IgA molecule as it passes through these cells. IgM, normally present in serum as a pentamer, is the immunoglobulin class produced early during a primary antibody response to an antigen.

Evaluation of immunoglobulins consists of qualitative and quantitative tests that are useful for evaluating immunoglobulin classes and their subclasses and/or antigen-specific antibody. Age-dependent change in the levels of immunoglobulins must be taken into account when interpreting results. Decreases in the level of a serum protein, such as an immunoglobulin, can result from impaired synthesis, altered utilization, and/or increased loss. Immu-noglobulin molecules of a particular class or subclass all share the same chemical structure, are recognized by a common

structure in the constant region of the heavy (or light) chain, and, as such, can behave similarly in an immunoas-say. The variable region of a specific antibody reacts with an antigenic epitope that is part of intact molecular structure of the antigen, conferring the "specific" nature of the antibody. Binding of the antigen to specific antibodies is also defined by a qualitative aspect of strength of the binding between antibody and antigen (defined by affinity for one interaction and avidity for the combined affinities in the case of multiple epitopes), making quantitative measurement of specific antibodies more difficult.

A. Qualitative Assessment (Electrophoretic Methodologies)

1. **Zone electrophoresis.** This technique allows for the separation of proteins based on electrical charge. The sample (solution) to be tested is placed on a buffer-saturated support medium (e.g., paper, agarose) and subjected to an electropotential gradient. **Serum electrophoresis** normally yields five bands consisting of albumin, alpha-1, alpha-2, beta, and gamma globulin fractions (Fig. 20-1). These bands can be assessed with a densitometer that generates a tracing from which the relative percentage of each fraction is determined. Immunoglobulins normally fall in the gamma globulin band, although they also migrate into the beta and alpha-2 globulin bands. Zone electrophoresis can be performed on other body fluids, including cerebro-spinal fluid (CSF) and urine. This semiquantitative technique is useful for assessing total protein status and can be used to screen for monoclonal immunoglobulins, although this technique may miss low-level monoclonal antibodies seen in early myelomas.

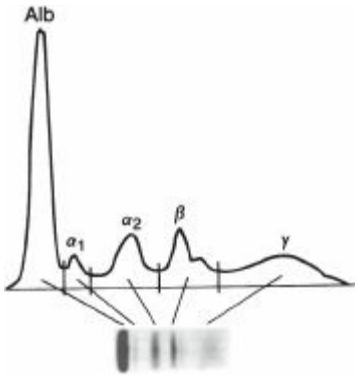

Figure 20-1. Zone electrophoresis. The electrophoretic pattern and densitometric tracing demonstrate the five major bands (albumin plus alpha-1, alpha-2, beta, and gamma globulins) from a normal serum sample.

2. **Immunoelectrophoresis (IEP)** is a two-step method in which proteins are electrophoretically separated in a gel and then antiserum, directed against one immunoglobulin heavy chain (α, δ, ε, γ, or μ) or one light chain (κ or λ), is loaded into a trough in the gel, and is allowed to diffuse into the gel containing these separated proteins. The antibody combines with the appropriate protein (immunoglobulin), resulting in the formation of a precipitin arc(s) of the antibody–antigen complex in the area of the gel where antigen and antibody concentrations are at equivalence. This has been used primarily for the characterization of monoclonal immunoglobulins, but in the clinical laboratory, this method is now largely replaced by immunofixation electrophoresis.
3. **Immunofixation electrophoresis (IFE)** uses zone electrophoresis, followed by overlaying of the electrophoretically separated proteins with antibodies directed against specific immunoglobulin heavy or light chains. This results in immunoprecipitation of the

antibody–antigen complex (at equivalence), which can then be stained (e.g., imido black) and visualized (Fig. 20-2). Polyclonal immunoglobulins give a diffuse band, a monoclonal immunoglobulin produces an intense narrow band typically within the diffuse band in the background, and oligoclonal immunoglobulins yield multiple bands of increased intensity against the background. This technique is easier to interpret and more sensitive than IEP, though it is not quantitative. The test currently represents the standard clinical laboratory approach for identification of monoclonal or oligoclonal immunoglobulins.

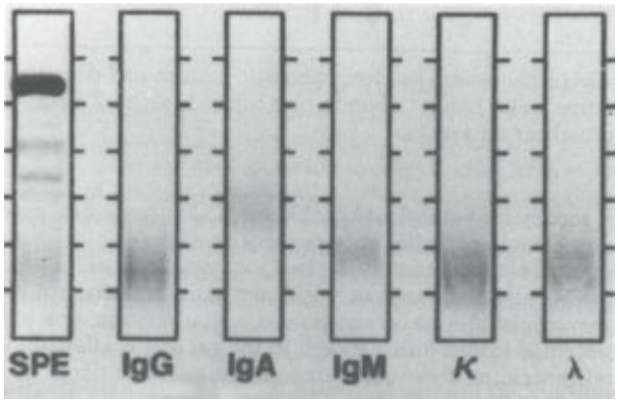

Figure 20-2. Immunofixation electrophoresis. Demonstrates a normal pattern with antibodies to the major heavy-chain and light-chain proteins. A clonal immunoglobulin would result in a darker staining band in a heavy-chain and light-chain zone.

B. Quantitative Assessment (Precipitin Methodology)

1. **Double gel diffusion** is another semiquantitative test that evaluates the relationship between specific antibodies or antigens in solutions. Comparison between a reference material and unknown serum allows a comparative assessment for identity, partial identity, or nonidentity. Although it lacks the detection sensitivity of many quantitative methods, the test is technically easy, can be performed with antigen preparations that are only partially purified, is highly specific, and serves as a useful screening test for the presence of an antibody or antigen particularly in a heterogeneous sample. However, this method currently is used infrequently in clinical laboratories.
2. **Single radial immunodiffusion** allows quantification of a protein (antigen) by adding serum (or other fluid) to wells cut into agarose that contains a specific antiserum. An immunoprecipitin ring of immune complexes is formed as the relevant serum protein (antigen) diffuses into the antibody containing agarose and precipitates once it reaches the region of antibody–antigen equivalence. Thus, the diameter of this ring is proportional to the concentration of the protein (antigen) being evaluated because the concentration of the antiserum is constant throughout the gel. The concentration of the unknown is then determined by plotting the precipitin ring diameter on a concentration curve produced from a series of standards with known protein (antigen) concentration. **Radial immunodiffusion (RID)** is a simple and reliable method to quantify immunoglobulins (including IgG subclasses), complement components (e.g., C3, C4, and factor B), and other proteins. At least three situations may result in erroneous results using conventional RID kits: (i) **low-molecular-weight or monomeric IgM** (e.g., Waldenström's macroglobulinemia and ataxia telangiectasia) can be reported incorrectly high due to the more rapid diffusion of the low-molecular-weight IgM compared with the heavier pentameric IgM standard; (ii) **high concentrations of IgG rheumatoid factor** can

produce complexes of IgG that diffuse more slowly than the IgG standard, resulting in an underestimation of the IgG level; and (iii) **the presence of antibovida (e.g., goat) species–directed antibodies**, which may be seen in IgA-deficient patients, that can bind the antiserum (in the agarose), if it is from a Bovidae source, yielding a false-positive result.

3. **Nephelometry** is a method to quantify proteins in a solution that is based on the scattering of light from soluble immune complexes generated by the addition of specific antibody to the sample being tested. In contrast to precipitin reactions, nephelometry is performed in slight antibody excess, and this procedure is readily amenable to automated instrumentation. There are two general approaches, rate and fixed-time nephelometry, both of which enable accurate measurement of IgG and IgG subclasses, IgA, IgM, C3, C4, factor B, C-reactive protein (CRP), and a number of other serum proteins. This method is adaptable for quantifying low-level proteins, including those in the CSF. Nephelometry is the standard method for quantifying immunoglobulin in most clinical laboratories because of the high-volume capabilities of modern nephelometers.

C. Quantitative Assessment (Immunometric Methodology)

1. **The radioimmunoassay** (RIA) was originally developed to measure insulin levels in serum. The original RIA was based on a competitive binding assay in which a constant amount of antigen-specific antibody was placed together with a small amount of radiolabeled antigen. Next, the sample, containing an unknown concentration of the antigen, was added. Antibody-binding antigen derived from the sample displaces the labeled antigen, and the decrease in radioactivity (in the immune antibody–antigen complexes) correlated with the concentration of the antigen in the sample.

   The competitive binding test can also be reversed by using a fixed concentration of purified antigen together with labeled antibody to evaluate for specific antibody concentrations in an unknown sample. A further modification of this method uses a **solid phase** to immobilize one of the reactants (antigen or antibody) and can be performed as an indirect or sandwich assay (see enzyme-linked immunosorbent assay [ELISA] below). RIA is a very sensitive method for specific protein quantification but has the disadvantage of requiring expensive equipment and relatively expensive radioactive reagents, which have defined and often limited shelf lives in addition to requiring special means for disposal.

2. **Enzyme-linked immunosorbent assay** (ELISA) is an immunoassay method that uses polystyrene plates, tubes, or beads as the solid phase to provide a binding site for the specific antigen under study. Serum (or other fluid) is added to the antigen-coated plate (tube, beads), which enables antibody to bind to the specific antigen immobilized on the solid phase. The presence of bound immunoglobulin from the sample is then detected following a wash step by using a second, enzyme-labeled antibody (reactive with the bound immunoglobulin). Following another wash step, the appropriate chromogenic substrate is added, resulting in enzyme-dependent generation of color (Fig. 20-3). The intensity of this reaction can be measured and is proportional to the antibody concentration present in the sample, derived from a so-called standard curve. The method can be altered using a “sandwich” technique to detect antigen with a test system that has antigen-specific antibody immobilized on the solid phase. This “capture” antibody is used to bind antigen

in an unknown sample. This is followed by a second antigen-specific antibody that is enzyme-labeled (Fig. 20-3). Addition of the appropriate chromogenic substrate will yield color that is proportional to the antigen concentration.

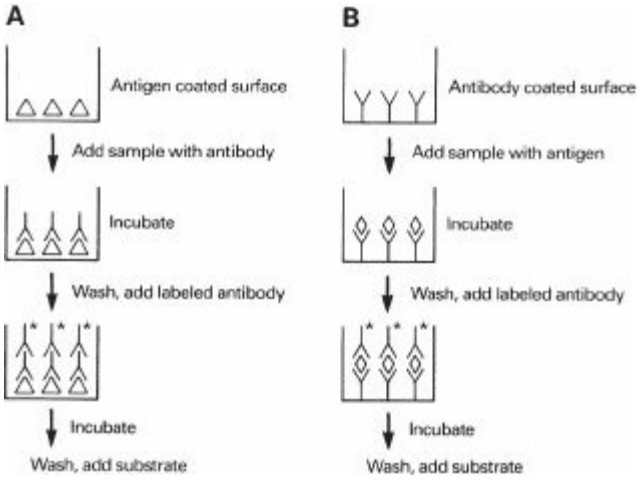

Figure 20-3. Solid-phase enzyme-linked immunosorbent assay (ELISA): **(A)** indirect assay; **(B)** "sandwich" assay. The label (*) on the antibody can be an enzyme plus substrate (as shown), a radionuclide (solid-phase radioimmunoassay), or a fluorochrome (solid-phase fluorescence immunoassay).

The sensitivity of an ELISA can be made comparable to that of an RIA. This method can be used for quantifying a number of specific antibodies or antigens and has the advantages of being simple to perform, requiring no radioactive isotopes, and having excellent reproducibility. It is currently the standard assay in many laboratories for antiviral antibody testing, including initial human immunodeficiency virus (HIV) antibody testing, and also testing for a number of other immunologic proteins (including IgG subclasses, IgE, autoantibodies). Alternatives to the enzyme-based test system include immunoassays that employ either a fluorescent or a chemiluminescent detection system. The latter approach has the advantage of providing amplification to the signal, extending the detection range of the immunoassay.

D. Other Assays for Protein Evaluation

1. **Immunoblot (Western blot)** is primarily a qualitative method to identify specific antibodies. In this technique, antigens of interest are separated using polyacrylamide gel electrophoresis. The separated proteins are then transferred to a nitrocellulose membrane. This is followed by overlaying the membrane with the antibody (e.g., serum) sample of interest and evaluating for the presence of bound immunoglobulin (specific antibodies) using a second labeled antibody (enzyme or fluorochrome) to human immuno-globulin. Although this method is not quantitative, it does allow for the detection of antibodies reactive with electrophoretically distinct protein antigens. The availability of commercial test kits has simplified the performance of these assays and has allowed the widespread use of the Western blot as a confirmatory test in assessing HIV serologic status and by many laboratories in characterizing the antibody response to *Borrelia burgdorferi* (Lyme disease). Other clinical laboratory applications of this technology are more limited at this time.
2. **Indirect immunofluorescence assays** usually use a tissue section or cell line on a microscope slide as a source of the antigen(s) of interest. The substrate is overlaid with the unknown sample, allowing any specific antibody to bind to the antigen(s). The

presence of bound antibody is determined with a fluorochrome-labeled antibody reactive with bound antibody, followed by visual examination using fluorescence microscopy. This method is commonly used to test for antinuclear antibody (ANA) and a variety of virus-specific antibodies. The technique is fairly sensitive, relatively quantitative, and technically simple to perform, although reading consistency between different operators can be problematic.

3. **Agglutination assays** typically are performed using either red blood cells or latex particles that are coated with the antigen of interest. The presence of antigen-specific antibody results in macroscopically detectable agglutination of the antigen-coated particles. These tests were previously used to detect antithyroglobulin and antimicrosomal antibodies (by hemag-glutination), rheumatoid factor (by latex agglutination), and various other antibodies. However, this method is not commonly used in the clinical laboratory because it is less sensitive than available immunoassays.

E. New and Emerging Assays

1. **Multiplex assays.** The development of scaled-down ("miniaturized") assays that are able to detect and measure multiple analytes simultaneously (e.g., antibodies, cytokines, etc.) has facilitated the study and management of human diseases and is best represented by multiplex bead array assays (MBAAs). A wide repertoire of tests, using both immunologic and molecular capture targets (ligands), has been developed for MBAA. These include, but are not limited to, determining allergen-specific IgE, infectious agents, antibodies, autoantibodies, cytokines, growth factors, and hormones, as well as a variety of molecular targets of interest (including genes and expression levels of genes). Commercially available MBAA systems may be performed on either multiuse flow cytometers or on more specialized platforms such as the Luminex system. The general principle of the MBAA, with regard to the "multiplexing" capabilities, is achieved through several related approaches. Differential intensities of a single fluorochrome ("color") or dual fluorochromes contained within the capture bead provide many unique combinations that determine the degree of multiplexing. Dual colors offer more targets/analytes to be measured but may need more sophisticated platforms, while single fluorochrome can often be adapted for a clinical cytometer that is already in use.

The beads with their unique spectral color (property, "address") are coated (tagged, immobilized) with an antigen/ligand that forms the target for detecting the analyte (such as an antibody or cytokine) in the serum/plasma (only small amounts of serum/plasma are typically required) of the individual being tested. The reaction is developed by subsequent detection of the captured ligand using a second "reporter" antibody in a high throughput and largely automated manner with sophisticated data processing and analysis.

MBAA technology differs from ELISA technology in the following ways: ELISAs do not use fluorescence as the read-out approach and, generally, measure only one analyte at a time (i.e., uniplex). As ELISA has been the prevailing (preceding) method for many analytes, it is necessary to compare both methodologies. For example, a key concern in the development of a clinically applicable MBAA is the possibility that the process of multiplexing itself introduces artifacts in the assay ("matrix" effect). Commercial kits are generally optimized to eliminate or minimize matrix effects (requiring strict adherence to

the manufacturer's protocols).

The correlations between multiplex (MBAA) and corresponding uniplex (ELISA) measurements are generally good, especially when identical capture and reporter substrates (antibodies), as well as similar reagents (e.g., diluents, serum blockers, etc.), are used. When developing MBAA assays for diagnosis or sequential monitoring of patients, the MBAA should first be compared to the existing methodology, and then use a consistent MBAA approach (kit, instrumentation, reagents).

2. **Luciferase immunoprecipitation systems (LIPSs).** Among the challenges faced when assessing antigen-specific antibodies is the need to know the nature of antigens and the generation of antibodies that are specific for those antigens. With infectious agents, it is often important to distinguish the pathogen-specific antigen(s) or epitope(s) that are relevant for protective immunity from the potentially vast array of epitopes/antigenic structures that are not. In addition, accurate detection of an antibody response to an infectious agent ("seroconversion") may depend on the conformational nature of the antigen(s), rather than strictly linear epitopes. Obtaining the antigens of interest from whole cell lysates of infectious agents or through recombinant technology may lead to cross-reactivity, high background activation or potentially, the use of antigens or antigenic structures that are not relevant *in vivo*.

The LIPSs assay is an emerging technology that can be used to address these challenges. With LIPSs, the combination of synthetic biology involving the engineering of proteins of interest and a novel immunoprecipitation technology allows antigen and antibody to interact with each other in solution, rather than bound to plates (solid phase), so that *in vivo* conformational relevance of the interaction can be mimicked *in vitro*.

On the synthetic biology side, artificial gene synthesis can generate multiepitope and chimeric proteins that better simulate how an antigenic structure, for example, derived from a pathogenassociated antigen, interacts with antibody *in vivo*. The proteins are generated using mammalian expression vectors. Advances in proteomics will expand the ability to generate antigens/proteins that can be used to detect antibodies in biologic samples. In order to develop an immunoassay, the proteins are fused with a luminescent enzyme (Renilla luciferase) that produces a light signal when exposed to its substrate (e.g., coelenterazine).

The combination of selecting mammalian cells to generate recombinant proteins and allowing the proteins and (patient-derived) antibodies to interact in solution enhances the sensitivity of the assay with dynamic ranges that are substantially higher than that obtained by traditional ELISA technology. Similarly, the same technology can be used to develop immunoassays that can detect and measure autoantibodies and tumorassociated antibodies.

II. EVALUATION OF LYMPHOCYTES

A. Characterizing Lymphocytes

Flow cytometry provides a methodology for multiparameter analysis of blood cells at the single-cell level. It is the most versatile platform to study the human immune system and is commonly used for the identification of human lymphocyte subsets, a method referred to as

immunophenotyping. Immunophenotypic studies provide insights into the differentiation and function of human lymphocytes and identification of novel lymphocyte subsets, such as natural killer T cells (NK T cells), Th17 T cells, among many others. An (ever) increasing repertoire of monoclonal antibodies, specific for lymphocyte-specific antigens, allows for continually increasing the types of cells that can be evaluated. Along with advances in instrument operation, automation, data analysis, and fluorochrome chemistry, multiparameter analysis (up to 15 or more parameters per individual cell) is possible.

B. Principles of Flow Cytometry

1. **Monoclonal antibodies** are produced by fusing an immortal murine myeloma cell line with normal murine plasma cells to yield hybridoma cells that effectively are immortal and can be selected for appropriate antibody specificity before cell expansion. This approach leads virtually to an unlimited supply of antigen-specific antibodies. There is an ever-increasing number of monoclonal antibodies to lymphocyte cell surface antigens, which are categorized according to a **cluster of differentiation (CD) numerical convention** (Table 20-1, http://en.wikipedia.org/wiki/%20List_of_human_clusters_of_differentiation). These reagents allow for significant progress in the understanding of lymphocyte differentiation and maturation. In addition, other monoclonal antibodies yield information about mechanisms of cell adhesion and activation. In the area of lymphocyte phenotyping, monoclonal antibodies enable more complete evaluation of cell lineage, differentiation, activation, and functional capacity. These reagents provide important pieces of information regarding the presence of particular cells and their potential function, but they do not evaluate the actual function of the cell. More recently, intracellular staining for specific proteins including cytokines has become a standard approach that supplements immunophenotyping.

Table 20-1 Lymphocyte Surface Antigens

T-cell surface antigens	
CD1	Found on cortical thymocytes
CD2	Alternative pathway for T-cell activation; SRBC receptor, also referred to as LFA-2, found on all circulating T cells
CD3	Multichain receptor associated with the T-cell antigen receptor (TCR); found on all circulating T cells
CD4	Cytoadhesion molecule for MHC (HLA) class II molecules; found on approximately two-thirds of the circulating T cells
CD5	Single-chain molecule found on most circulating T cells; also found on some B cells
CD7	Present on T-cell precursor and throughout T-cell differentiation
CD8	Cytoadhesion molecule for MHC (HLA) class I molecules; found on approximately one-third of the circulating T cells
CD25 (Tac, IL-2R, p55)	Alpha chain of the interleukin-2 (IL-2) receptor; found on activated T cells and B cells
CD28	Mediates a comitogenic signal for T-cell proliferation; found on most $CD4^+$ T cells and a subset of $CD8^+$ T cells
CD38	Found on thymocytes, activated T cells, pre-B cells, activated B cells, and plasma cells
CD45RA	Isoform of the CD45 molecule found on "naïve" CD4 T cells and rare memory CD8 T cells
CD45RO	Isoform of CD45 found on "memory" CD4 T cells
CD95 (Fas)	Receptor that is a member of the tumor necrosis receptor superfamily that is expressed by activated T (and B) cells and induces lymphocyte apoptosis
CD154 (CD40 ligand)	Expressed by T cells following activation and interacts with CD40 on B cells to facilitate isotype switch and CD40 on monocytes in response to selected opportunistic organisms
B-cell surface antigens	
Surface immunoglobulin	IgM found on immature B cells; IgM and IgD is found on mature B cells; the appearance of IgG, IgA, or IgE develops later after isotype switching.
HLA-DR	MHC class II molecule found on all B cells, also present on monocytes and activated T cells
CD5	Present in low density on a B-cell subpopulation (presence of which is inversely related to age) and on the majority of B-cell CLL cells (also found at high density on most T cells)
CD10 (CALLA)	Found only on pre-B cells and on common acute leukemia cells
CD19	Expressed on pre-B cells and present throughout B-cell differentiation; augments B-cell proliferation
CD20	Present throughout B-cell differentiation but is expressed after CD19 appears on the pre-B cell
CD21	Complement receptor for C3d (CR2), also is the EBV receptor, found on the majority of circulating IB cells
CD22	Found on the majority of circulating B cells, also found in high density on hairy cell leukemia cells
CD23	Low-affinity IgE Fc receptor (FcεRII)
CD32	IgG Fc receptor (FcγRII)
CD40	Interacts with CD40 ligand (CD154) on T cells; activation enables B cells to undergo isotype switching; also present on monocytes
CD72	Expressed on very early B cells and lost during differentiation; CD5 ligand
NK-cell surface antigens	
CD2	Found on 40%–70% of NK cells
CD8	Low-level expression found on 30%–50% of NK cells
CD16	Low-affinity IgG Fc receptor (FcγRIII)
CD56 (NKH-1)	Found on the majority of NK cells, also found on a small subset of T cells that function as non-MHC-restricted cytotoxic cells
CD57 (HNK-1)	Found on ~50% of NK cells, also found on T-cell subpopulations

CD1, cluster of differentiation 1; SRBC, sheep red blood cell; LFA-2, leukocyte function–associated antigen 2; MHC, major

histocompatibility complex; HLA, human leukocyte antigen; IgM, immuno-globulin M; CLL, chronic lymphocytic leukemia; EBV, Epstein-Barr virus; NK, natural killer.

2. **Fluorochromes** are compounds that absorb light of a defined wavelength and convert this energy into light of a longer defined wavelength (lower energy). There are currently a wide range of fluorochromes routinely used in clinical phenotyping including **fluorescein isothiocya-nate (FITC)**, **phycoerythrin (PE)**, and **peridinin chlorophyll protein (PerCP)** that are excited by blue light (488 nm), with FITC generating green, PE emitting orange, and PerCP producing red light. Additionally, allophycocyanin and double (tandem) fluorochromes, which rely on energy transfer from one component to the other, are exciteable by blue and red light lasers, which now come standard in most benchtop flow cytometers, extending the number of colors available for clinical use. Other fluorochromes, including amcyan, pacific blue, and quantum dot nanocrystals, are used primarily in research settings because they require a violet or ultraviolet excitation source or specialized filter sets.
3. **The flow cytometer** is an instrument that allows for the rapid evaluation of multiple fluorescent and nonfluorescent measurements on a large number of cells in a solution. This enables assessment of multiple cell surface characteristics (parameters) for each cell, which can provide population and subpopulation information. The combination of multiple parameter assessment on each individual cell, together with a rapid analysis, provides significant advantages over conventional fluorescence microscopy. In addition, this type of instrumentation can be used to evaluate intracellular parameters using a variety of newer fluorescent probes as well as total cellular DNA as part of cell cycle analysis. Briefly, the machinery consists of four major elements: optics, fluidics, electronics, and a computer (with specific software). The optical system uses monochromatic light sources (typically lasers) that provide the excitation energy. The optical bench collects light derived directly from each cell as it passes through the laser beam(s). Each cell emits nonfluorescent (forward and side scatter) as well as fluorescent signals if one or more fluorochrome-conjugated monoclonal antibodies are bound to the cell. The two nonfluorescent parameters collected provide an index of cell size (forward light scatter) and a measure of cell granularity/ regularity (side-angle light scatter). The combination of these two parameters allows for a "three-part leukocyte differential," which in nonmalignant settings easily distinguishes between lymphocytes, monocytes, and granulocytes in a whole blood sample following red blood cell lysis.

The fluorescent signals result from cell surface or intracellular binding of specific monoclonal antibodies conjugated directly to fluo-rochromes that, following excitation by a specific wavelength, emit light of lower energy. The availability of multiple fluorochromes excited by the same wavelength with emissions of different wavelengths facilitates the use of multiple reagents simultaneously for a multicolor study with a single light source. A second laser is typical in most clinical instruments, facilitating additional "colors," and three laser instruments have become more common for clinical studies, readily allowing eight "color" studies. These polychromatic studies often include reagents that combine evaluation of cell surface and intracellular targets.

Current instrumentation provides graphical displays of cell frequency versus light intensity as a single-parameter histogram. Alternatively, the signal intensity of two parameters ("colors") can be

plotted versus cell frequency using a dot plot or a contour plot. Multiple parameters in a polychromatic study are generally evaluated using sequential two-color displays that progressively subdivide specific cell subpopulations. Typically, 10,000 to 20,000 cellular events are collected to provide sufficient numbers for meaningful data in the evaluation of subpopulations of interest. However, when cells of interest are in low abundance, collection of larger cell numbers is required. For more on instrumentation and a general discussion of the principles of flow cytometry, see: http://en.wikipedia.org/wiki/Flow_cytometer.

C. Lymphocyte phenotyping utilizes fluorochrome-conjugated monoclonal antibodies directed at specific cell surface antigens and flow cytometry to differentiate lymphocyte subpopulations. Multiple fluorochrome-conju-gated monoclonal antibodies are added to small volumes of whole blood, the red blood cells are lysed, the sample is washed, and the cells are evaluated by the flow cytometer. The proper characterization of lymphocytes requires differentiating these cells from the other leukocytes (i.e., mono-cytes and granulocytes) in a process called **lymphocyte gating.**

The data generated from lymphocyte phenotyping are expressed both as the percentage and absolute number of each cell subpopulation evaluated. In addition, data must be interpreted in the context of appropriate controls, because normal phenotypes vary with age, race, and sex. A simple approach to validate results depends on the axiom "the whole is the sum of its parts" (T cells + B cells + NK cells = 100%). This simple check can be applied to any phenotyping study that reports all three major lymphocyte groups. In normal adults, approximately three-fourths of the circulating lymphocytes are T cells, with the **ratio of CD4 cells to CD8 cells normally 1.5 to 2.0:1,** and the remaining non-T lymphocytes are generally equally divided between B and NK cells.

The most commonly requested flow cytometric test is a CD4 count used to obtain prognostic data regarding HIV infection and to make decisions regarding therapy. The evaluation of clonal excess, cell lineage, and state of differentiation by flow cytometry is a standard approach in the assessment of leukemia and lymphoma. Additional applications of this methodology include evaluation for absence of cell populations or subpopulations in specific immune deficiencies (Fig. 20-4) or increased levels of cell activation in a variety of immunologically mediated diseases. Flow cytometry generally does not provide diagnostic data, but rather supportive information, and in many settings, it is used for investigative types of studies.

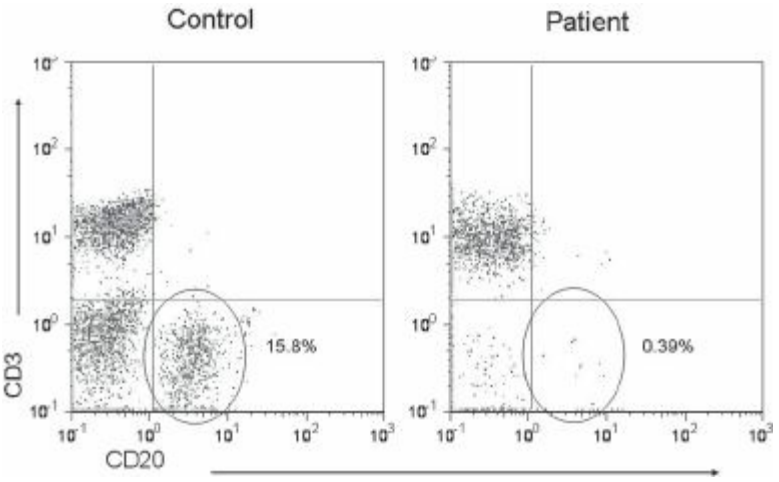

Figure 20-4. Flow cytometric evaluation of CD3 versus CD20 from a control individual (**left panel**) and a patient with X-linked agammaglobulinemia (**right panel**, absent B cells).

D. Intracellular Flow Cytometry

1. Protein Detection

Some exceptions exist to the principle that flow cytometry does not generally provide diagnostic data. In general, any genetic defect that results in absent or decreased protein expression can be detected by flow cytometry if the appropriate monoclonal antibody reagents exist. Although this is most often applied to intracellular flow cytometry, it also applies to "regular" immunophenotyping approaches (e.g., lack of major histocompatibility complex (MHC) Class II expression in the bare lymphocyte syndrome).

A central question regarding the use of protein detection concerns the ability of an antibody to detect protein when the genetic variation does not result in complete lack of the translated protein product. It is important to understand the sensitivity of detecting abnormal gene products, particularly those that reflect missense mutations. Determination of specificity is also relevant as reduced expression of the protein in question in the absence of a genetic defect is not necessarily a false-positive result but may be a consequence of other defects, including defects in gene regulation, epigen-etic regulation, transcription, and stability of message RNA.

Protein detection by flow is a useful tool for screening and diagnosing primary immunodeficiency disorders. Intracellular evaluation includes detection of BTK protein (in monocytes) to diagnose X-linked agammaglobulinemia (see Fig. 20-4), WAS protein to diagnose Wiskott-Aldrich syndrome, perforin to diagnose familial hemophagocytic lymphohistiocytosis, and SAP protein to diagnose XLP, among others (see Chapter 18, Primary Immunodeficiency Diseases).

Important advantages of this methodology are fast turn-around times, low costs (as compared to genetic testing), and relative ease of testing. In addition, in cases in which genetic results are ambiguous, protein detection by flow may help providing relevance and significance to genetic data.

2. **Functional flow cytometry** has seen significant advances as well. It can be used as a read-out system in traditional lymphocyte function (e.g., proliferation) assays, as discussed below. This can be based on detection of blastogenesis (increased size), activation markers (e.g., HLA-DR, CD25, CD69), or incorporation of nucleoside analogues of thymidine that are incorporated into DNA during the S phase of the cell cycle (e.g., bromodeoxyuridine). Functional flow cytometry can be more sophisticated and, if combined with additional markers (surface molecules) of interest—the premise of multiparameter analyses—reveals complex functional characteristics of lymphocytes that, in certain cases, can define specific diseases or specific pathogenic mechanisms. Examples include intracellular detection of cytokines (e.g., IL-17 in Th17-defined T cells), as well as intracellular detection of phosphorylated proteins that are reflective of specific signal transduction pathways used by cells at baseline or under defined stimulation conditions.

III. FUNCTIONAL EVALUATION OF LYMPHOCYTES

A. *In Vitro* Studies of T-cell Function

1. **Proliferative assays** generally focus on T-cell proliferation that is evaluated by assessing DNA synthesis in cultured lymphocytes following one or more stimuli. These stimuli include polyclonal activators (mitogens including phytohemagglutinin [PHA] and concanavalin A [conA]) and antigens (alloantigens or exogenous recall antigens such as tetanus toxoid). At the end of the response period, proliferation is evaluated by quantifying the incorporation of a radioactive-labeled nucleoside (e.g., tritiated thymidine) into newly synthesized DNA. The results are usually expressed as counts per minute (cpm) or disintegrations per minute (dpm) or as a stimulation index (cpm of stimulated cells divided by the cpm of unstimulated cells). Other read-out systems not based on radioactive thymidine can be used as well.

   Mitogen stimulation activates a significant proportion of normal T cells and can be assessed after 3 days of culture, whereas antigen stimulation is limited to T cells with the specific antigen receptor and is evaluated at 6 or 7 days. A panel of antigens should be used to increase the likelihood that the patient has had prior exposure to at least one of the test antigens. When whole blood assays are used for testing lymphocyte proliferation rather than separated mononuclear cells, it is important to consider the absolute lymphocyte count because this can significantly affect the results. Studies of patients with HIV infection have demonstrated that unresponsiveness to recall antigens can be present early when there is a relatively subtle T-cell disorder. Progression of the T-cell defect is associated with loss of T-cell response to alloantigens, followed by loss of the response to PHA. The reversed sequence of events is typically seen after bone marrow transplantation, reflective of (improving) immune reconstitution.

   The extent of T-cell deficiency may be reflected by the degree of the proliferative defect, with PHA unresponsiveness indicating a profound T-cell abnormality. Although counter-intuitive, in some patients with T-cell abnormalities, responses to antigens remain intact, while responses to mitogens are decreased. This reflects the complexity of the immune response and the nature of *in vitro* testing. Therefore, assessment of T-cell function should be based on all available data, including immunophenotypic data together with functional data.

2. **Cytotoxicity** testing evaluates the capacity of T cells to kill target cells in either MHC-restricted or in non-MHC-restricted assays. The assay most commonly is used to test MHC-restricted, a/b+ T-cell receptor (TCR), $CD8^+$ T cells that recognize endogenously processed antigens (i.e., viral antigen or alloantigen) in the context of class I MHC molecules (HLA-A, B, or C molecules). $CD4^+$ cytotoxic T cells recognize antigens in the context of class II MHC molecules, whereas g/d+ TCR T cells typically mediate non-MHC-restricted T-cell cytotoxicity.

   In standard assays, the target cells are labeled with a radioactive probe, and T-cell lysis of the target cell is assayed by measuring radioactivity released into the cell-free supernatant. In MHC (HLA)-restricted systems, the T cells must have prior exposure to the antigen in order to generate active cytotoxic cells. This type of T-cell response is particularly important for host defense against viruses and other intracellular pathogens. Non-MHC-restricted T-cell cytotoxicity is mediated by a small percentage of the circulating T cells and is very similar to NK cell cytotoxicity because it does not require

prior sensitization (see Section IIIC, Natural Killer Cells). The *in vitro* cytotoxicity assay system used to test all forms of cytotoxicity utilizes a similar technique in which labeled target cells are mixed with the effector cells at varying effector to target ratios, and the degree of lysis is quantified in comparison to known normal cells.

Limitations to the utility of these assays include their technical difficulty, the potential of inducing artifacts associated with the initial phase of stimulation of T cells with the target in question, followed by a second phase to induce and measure actual killing of the target. When interpreting results, the possibility that cells may have been stimulated *in vivo* must be taken into consideration as this can affect *ex vivo* stimulation. Thus, in cases of (suspected) infections, test results should be interpreted with caution, and assays should be repeated under different circumstances (e.g., when an infection has been cleared).

3. **Soluble products** are produced by activated lymphoid cells and can be assessed in the cell-free supernatant following cell stimulation and culture. Assay methods for measuring these proteins (e.g., cytokines) include commercially available immunoassays, including multiplex assays and functional assays, which are technically more complicated. The evaluation of cytokine levels *in vivo* is complicated because of the short half-life of most cytokines and the high-affinity binding of these proteins to their cell receptors. An alternative method evaluates the presence of cytokines in the cytoplasm of lymphocytes following a short-term *in vitro* activation with mitogen (e.g., phorbol myristate acetate [PMA] and ionomycin) or antigen that is followed by intracellular fluo-rochrome-labeled antibody staining for specific cytokines and detection by flow cytometry. This method can also be adapted to look for antigen-specific T cells (see Section III.A.4. below).
4. **Antigen-specific T cells.** There is a steady increase in new methodologies for enumerating and characterizing antigen-specific T cells and their effector functions. There is a need for accurate, sensitive, and specific, as well as reproducible, data for measuring antigen-specific T cells in HIV and other infections, cancer vaccine development, and autoimmune diseases. In addition to direct *ex vivo* visualization and enumeration of these cells, functional correlates (*ex vivo*, *in vitro*) are needed to assess the overall efficacy of current and future therapies in these settings.

Functional flow cytometry can be used to evaluate intracellular cyto-kine secretion in response to antigen exposure in antigen-specific T cells. In addition, measurement of antigen-specific T cells can also be performed using ELISA and ELISPOT technology.

Antigen-specific T cells can be enumerated using limiting dilution analysis (LDA). This technically difficult assay estimates the precursor frequency of a particular T-cell population and can be used to measure specific cytotoxicity of the cells (CTL). Alternatively, LDA-cultured cells can be assayed by cytokine secretion in the supernatant (helper T cells). There are several limitations to the use of this technology, including the need for large volumes of starting material (>50 mL of blood), the arbitrary distinction of positive and negative wells (cultures), and the requirement for cell differentiation, expansion, and survival during the culture period, which together drive selection and underestimation of the number of antigen-specific T cells; such underestimation has been validated by antigen-specific T-cell analysis. MHC/peptide complex technology allows for direct visualization, enumeration, and characterization of antigen-specific T cells *in vivo*.

The main limitation of this technology is the need to know HLA restriction of the peptide, linked to the appropriate HLA alleles that are not present in all patients. No prior knowledge regarding peptide configuration and its HLA specificity is needed for two other methods of enumeration of antigen-specific T cells: measurement of intracellular cytokines in T-cell subsets by flow cytometry and measurement of secreted cytokines by ELISPOT technology. In both intracellular cytokine detection by flow cytometry (IC-FCM) and ELISPOT detection, T cells are cultured and activated (for several hours to days) *in vitro* with the antigen of interest (e.g., recall antigen, tumor-derived antigen). Furthermore, T cells can be recovered in both assays for subsequent studies (e.g., gene profiling). In the IC-FCM assay, cytokines of interest are visualized inside cells, dependent on the addition of protein transport inhibitors (e.g., monensin). Variation of culture time can be used to select for existing (*in vivo*) memory cells, if the culture period is limited to several hours, or to select naive T cells if cultured for days.

ELISPOT is a variant of ELISA technology. Cytokines produced by cultured antigen-specific T cells are secreted upon which they are bound by primary antibodies that have been immobilized in ELISPOT wells. Secondary antibodies conjugated to color-producing enzymes capture the cytokines immobilized by the primary antibodies. ELISPOT technology seems the most sensitive technique to detect antigen-specific T cells, especially if IFN-γ and TNF-α are measured.

B. Natural killer (NK) cell–mediated cytotoxicity does not require prior sensitization of the effector cells. Susceptible target cells consist of a number of different cell lines, and the assay system is identical to the approach described in Cytotoxicity (see Section III.A.2. above). The NK cell is one of a number of different cell types that mediate a cytotoxic function referred to as antibody-dependent cellular cytotoxicity (ADCC). In this process, the cytotoxic effector cells are bound via their IgG Fc receptors to the IgG antibody–coated target cells. This increases the range of susceptible target cells and can be tested in a standard cytotoxicity assay system using antibody-coated targets. The NK cell appears to be important in responding to viral infections, graft rejection, and tumor rejection. Absence of NK-cell activity is very rare, although diminished function can be seen in a number of clinical situations, including patients with X-linked lymphoproliferative syndrome, hemophagocytic disorders, and with cancer.

C. Evaluation of the Toll-like receptor (TLR) system focuses on receptors that are part of the innate immune system and recognize specific pathogen-associated molecules (patterns, motifs). Their role is to activate phagocytes and tissue dendritic cells to respond to pathogens (danger) by secreting chemokines and cytokines and to express molecules important in moving from an innate immune response to an adaptive immune response. Genetic defects affecting the TLR pathway have been identified in patients with unique patterns of infections. These include IRAK4, MyDD88, TLR3, UNC93B and NEMO mutations. Testing of the TLR pathway and the relevant components to screen for mutations in these (and other) genes is an emerging area of diagnostic immunology that is currently offered in few laboratories.

The basic principle of *in vitro* TLR testing is to stimulate cells (isolated mononuclear cells or whole blood) with the TLR ligands (agonists) that are specific for the particular TLR. For example, TLR4 is engaged by LPS, while TLR3 and TLR9 are stimulated by dsDNA and unmethylated CpG DNA, respectively. The read-out is production of cytokines in the supernatant or downregulation of

CD62L expression on granulocytes. As with all functional assays, care should be used when interpreting data, since many aspects of TLR function (*in vivo*) are poorly understood. For example, normal test results may not indicate that the TLR system is normal, if additional data, particularly with respect to the infection profile, suggest otherwise.

D. *In Vitro* Assessment of B Cells

1. Quantitative immunoglobulin levels are the first-line screening when evaluating B-cell function. The most common method used to evaluate immunoglobulin levels is automated nephelometry (see above). Results must be interpreted with age-matched controls because there are significant changes with age (see Appendix III) as well as minor differences based on sex and race. Most reference ranges have a 95% confidence interval (i.e., 2.5% of controls are above and 2.5% are below the range).

2. Immunoglobulin G subclass levels are performed to detect more subtle abnormalities in B-cell function. This may be clinically important in certain patients with recurrent infections who have normal or modestly decreased total IgG levels but have selective depression of one or more IgG subclasses. IgG subclass testing is moderately expensive and should be reserved for investigating cases with a history of recurrent bacterial infections that are strongly suggestive of an immune disorder in conjunction with a normal or low normal total IgG level. Because individuals with IgG subclass deficiency may be clinically well, identifying a decrease in IgG subclasses still requires demonstration of specific antibody production.

3. Specific antibody production evaluates B-cell immunity by determining the *in vivo* antibody response to specific antigens. This approach consists of measuring pre- and postimmunization titers to protein antigen (e.g., tetanus toxoid, diphtheria toxoid) and polysaccharide antigen (e.g., pneumococcal polysaccharide [Pneumovax®]). Quantification of antibodies to these antigens is available through selected commercial laboratories and may be available through state health laboratories. These studies help provide definitive evidence for an abnormality in B-cell function and, in the absence of panhypogammaglobulinemia, give critical information before initiating immunoglobulin replacement therapy. Differentiating normal from abnormal responses to polysaccha-ride antigens in young children (especially 2 to 4 years of age) remains unclear and should be considered in the context of the clinical circumstances. Conjugated vaccines, such as Prevnar, cannot be used to determine the specific response exclusively to polysaccharide antigens.

4. *Ex vivo* evaluation of B-cell function consists of testing B cells for the capacity to undergo proliferation, terminal differentiation, and immu-noglobulin secretion following nonspecific (mitogen) or specific (antigen) stimuli in a culture system. These studies, generally performed in investigational laboratories, are reserved for research applications.

IV. FUNCTIONAL EVALUATION OF PHAGOCYTIC CELLS

A. Monocyte/macrophage function can be evaluated for a number of specific functions, including antigen presentation for T-cell proliferation, ADCC, tumor cell cytotoxicity,

chemotaxis, and microbial killing. In addition, cytokine production can be evaluated following monocyte activation. These tests evaluate the monocyte role in antigen processing and presentation, tumor cell cytotoxicity, microbial phagocytosis, cytokine receptor expression, and elaboration of cytokines. The clinical indications for testing monocyte function include deficiency of T-cell function and unusual or atypical infections with opportunistic, intracellular microorganisms.

B. Neutrophil function can be separated into specific aspects of cell function including chemotaxis, phagocytosis, generation of the oxidative burst, microbial killing, and presence of surface adhesion molecules.

1. Neutrophil chemotaxis can be studied by isolating peripheral blood neu-trophils and using a **Boyden's chamber**. This device is designed with a filter that separates the cells from the chemoattractant (e.g., C5a) or control material. After a predetermined period of time, the filters are removed and examined for the presence of neutrophil migration in response to the che-moattractant. An alternative approach involves evaluating chemotaxis in a soft agar system in response to standard chemoattractants. *In vivo* chemo-taxis can be studied with the **Rebuck skin window method**. With this test, the skin is abraded with a scalpel, and a laboratory cover slip is placed over the abraded areas for 24 hours. The cover slip is then stained and analyzed microscopically. An immune deficiency may be present if there is an abnormality of neutrophils or monocytes displayed either by their absence or their inability to migrate to intracellular sites of antigen within 12 hours. Abnormalities of chemotaxis have been found in the **Chédiak-Higashi syndrome**, the **Pelger-Huët anomaly**, and some patients with the **hyper-IgE syndrome**. Demonstration of a significant decrease in neu-trophil response to chemoattractants *in vitro* is usually associated with a diminished inflammatory response *in vivo*.

2. The oxidative burst is the process that follows neutrophil activation and phagocytosis and results in increased hexose monophosphate shunt activity, oxygen consumption, hydrogen peroxide production, and superoxide radical formation. Functional testing of this process can be performed using the **nitroblue tetrazolium (NBT) test**, the **dihy-drorhodamine 123 (DHR) assay**, or the **chemiluminescence assay**. In the NBT test, activation of the neutrophils induces phagocytosis of the NBT dye. The oxidative burst, associated with activation and phagocytosis, reduces the NBT dye within the cell and generates blue insoluble crystals of formazan, which can easily be detected by microscopic examination. **Absence of NBT dye reduction is a pathognomonic finding in patients with chronic granulomatous disease (CGD)**. A more quantitative test uses an intracellular fluorochrome, dihydrorhodamine 123 (DHR), which upon contact with intracellular hydrogen peroxide is oxidized and emits a fluorescent signal that can be detected using a standard flow cytometer. The dye-loaded granulocytes are activated with PMA and evaluated for increased fluorescence within 15 minutes of exposure to the stimulus. The **DHR assay is extremely accurate in diagnosing patients with CGD and X-linked carriers of CGD** (Fig. 20-5). It is useful in monitoring myeloid chimerism following bone marrow transplantation in CGD patients. An alternative test involves evaluation of chemiluminescence, the

oxidative burst–dependent generation of light energy by activated neutrophils. Addition of ingestible particles (such as zymosan) activates neutrophils and induces phagocytosis, which results in the release of light energy. The chemiluminescence obtained with patient cells is measured and compared with the response obtained from normal cells. The results from this method usually parallel the findings of the NBT test and the DHR assay.

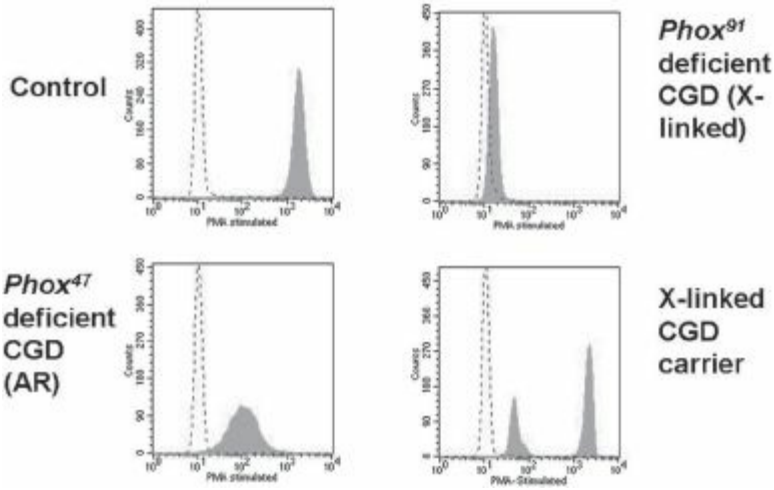

Figure 20-5. DHR assay of granulocytes 15 minutes after activation by phorbol myristate acetate (PMA). The upper panel represents control granulocytes demonstrating a normal oxidase response (upper left panel). In contrast, the granulocytes from an X-linked CGD (upper right panel) demonstrate virtually no oxidase activity, while those from an autosomal recessive CGD patient show a markedly reduced level of oxidase activity (lower left panel) and those from an X-linked recessive carrier have two populations of granulocytes (lower right panel) reflecting that there is a mixture of normal and abnormal cells in the circulation that is a result of random X chromosome inactivation (Lyonization).

3. Microbial killing assays mix neutrophils with opsonins and bacteria *in vitro* to evaluate actual killing of specific microorganisms. Different types of microorganisms can be used in the evaluation of killing. Cells from patients with CGD demonstrate markedly diminished killing of *Staphylococcus aureus* in this assay. The accuracy of this test depends on well-defined controls and an experienced laboratory.

4. Adhesion molecule assessment is directed at identification of three specific cell surface receptors on neutrophils: leukocyte function– associated antigen 1 (LFA-1), Mac-1, and p150/95. These can be identified by flow cytometry using monoclonal antibodies to the individual α chains (CD11a, CD11b, CD11c) and to the common β chain (CD18) that is part of the three heterodimeric adhesion molecules. Patients with leukocyte adhesion defects (LAD) have a defect in CD18 that manifests as decreased or absent expression of these surface antigens in both resting and activated neutrophils. Additional features in this disorder include the presence of peripheral neutrophilia and reduction of cell adherence, chemotaxis, and phagocytosis. Because the neutrophils of patients with LAD fail to move to the site of inflammation and are functionally deficient, the clinical features include recurrent infections, delayed wound healing, and absence of pus at infection sites.

V. THE COMPLEMENT SYSTEM

The complement system is comprised of circulating glycoproteins that are activated in a

cascade-like fashion. There are three different mechanisms of complement activation: the classical, the alternative, and the mannose-binding lectin pathway. The complement system is a part of the host defense through its lytic, chemotactic, and opsonic activity; its effects on catabolism of circulating immune complexes; and its role in immunoregulation.

A. Complement activity of the classical pathway can be evaluated with the total hemolytic complement (CH_{50}) assay. In this test, various dilutions of patient or control sera are added to sheep red blood cells that are bound (sensitized) by anti–red cell antibody (hemolysin). The serum provides a source of complement, and the degree of red cell lysis is plotted on a standard curve. CH_{50} results are reported as the inverse of the serum dilution that produces 50% red cell lysis. Currently, there are modifications of the traditional CH_{50} test that can detect unique components derived during complement activation to simplify the procedure. The biologic activity of complement components is labile, and **improper handling or storage of a serum sample can result in diminished complement activity**.

The CH_{50} is a very effective means of screening for the absence of a complement component and is particularly useful in diagnosing **terminal component** defects associated with recurrent neisserial infections. It is also frequently used to evaluate for complement activation, although it is less sensitive in this capacity. This approach is clinically used to follow patients with SLE and nephritis.

Assessment of the **alternative complement pathway** depends on the AH_{50} assay, which is a screening test for complement abnormalities in this pathway. This assay uses unsensitized rabbit erythrocytes (rather than sensitized sheep erythrocytes) as the target for lysis in a detection method similar to the CH_{50}. Evalution of the lectin pathway, via both quantitative and functional assays, can also be performed.

B. Complement component testing is usually included in the laboratory evaluation of immune-mediated inflammatory diseases and when there is a suspected genetic deficiency of one of the complement components.

1. **Immunoassays** for complement components are technically the simplest means of assessing their concentration and usually involve RID, immuno-assay, or nephelometric testing. Most clinical laboratories use these methods to assess complement components. This approach is fully satisfactory except in conditions that have a functionally deficient complement component that is antigenically indistinguishable from a normal complement component in the immunoassay. For example, in approximately 15% of patients with **hereditary angioedema**, the immunoassay for C1-esterase inhibitor yields normal levels of this protein because the abnormal protein is antigenically indistinguishable from the normal protein, yet the functional assay shows decreased or absent activity. In these patients, the functional assay (but not the immunoassay) correlates with the clinical findings.
2. **Functional assays** evaluate the actual activity of a complement component in an unknown sample. The indicator system is a CH_{50} assay that is constructed to contain all but one complement component. The unknown sample is the putative source of this component, and the degree of hemolysis is compared with that from a known normal. These assays are difficult and are generally performed only in specialized laboratories. The main use of this testing is to identify the actual component defect in an individual with clinical disease

and a depressed CH_{50}. Additional functional testing can be directed toward the various complement regulatory proteins, including the C1-esterase inhibitor.

C. Immune complex assays consist of a number of different techniques for determining the concentration of nonspecific antigen–antibody immune complexes in serum. Certain methods detect (bind) activated C3 and its cleavage products that are fixed to the antigen–antibody complex. In the **Raji cell assay**, immune complexes are immobilized with a cell line that has receptors for C3bi and C3d. In the **anti-C3 assay**, antibodies directed toward immune complexes fix C3, and in the **bovine conglutinin assay**, a bovine protein (conglutinin) binds immune complex–fixed C3. The next step involves addition of a labeled antibody to human immunoglobulin as the detection step for the immune complexes. An alternative approach is the **C1q binding assay** that uses the complement component, C1q, which is radiolabeled or immobilized on a solid phase to bind the immune complexes and allow for their detection. A solid-phase immunoassay system uses an antibody to C3 cleavage products to capture immune complexes that have the derivatives of C3; detection of the complexes depends on labeled antiimmunoglobulin antibodies. Although more than one method should be used to reliably detect circulating immune complexes, the clinical significance and utility of the results have not been clearly identified.

VI. NUCLEOTIDE-BASED TESTING

A. T-cell receptor excision circle (TREC) testing. T-cell differentiation and T-cell homeostasis are critical in maintaining immunologic health. Conversely, conditions in which these processes are abnormal often are associated with clinical immunodeficiency. Thymic integrity is an important requirement for normal T-cell differentiation and output. Flow cyto-metric immunophenotyping, particularly by using CD45RA and CD45RO expression on peripheral blood T cells, provides information about the status of thymic output. Another approach is the TREC assay. TRECs are episomal DNA structures that remain following the process of T-cell receptor rearrangement and are only found in T cells of thymic origin. Because TRECs are stable and not replicated when the cell divides, the amount of TRECs in a population of circulating T cells reflects its replication history. Thus, a naïve T cell—that has not been exposed to its antigen with instruction to divide—contains the maximum amount of TRECs, just as it exited the thymus. TRECs are used to estimate thymic integrity, thymic production, and thymic reserve/senescence.

Quantitative real-time polymerase chain reaction (PCR) is used to measure TRECs for assessing thymic function in primary immunodeficiency disorders that are caused both by stem cell defects or defects in thymus development (e.g., DiGeorge's syndrome), HIV infection, the response to antiviral therapy in HIV infection, aging, as well as monitoring T-cell immune reconstitution following stem cell transplantation and high-dose chemotherapy, or other T-cell depleting therapy.

Because TRECs are stable, TREC measurement is the method of choice in neonatal screening assays for severe combined immunodeficiency (SCID) and is now a standard newborn screening practice in many states.

B. T-cell spectratyping. TRECs are the "waste products" in the process of TCR rearrangement, a

process that creates the enormous diversity or repertoire of T cells and is mostly defined at the level of the complementarity determining region 3 (CDR3) of the variable regions of the TCR alpha, beta, gamma, and delta chain. Since the CDR3 is involved in binding antigen, analysis of the T-cell repertoire is another tool for monitoring immune function. Flow cytometry can be used to determine TCR variable beta (Vβ) chain usage (as represented by defined Vβ "families"), while the overall length of CDR3—the end result of varying numbers of D and J elements being used, D element reading frames, junctional diversity, and N region nucleotide addition—can be molecularly assessed by spectratyping. CDR3 spectratyping shows that the length of the CDR3 in a given TCR Vβ (or V-α) family represents a Gaussian distribution, varying between 1 and 11 amino acids (3 to 33 base pairs, respectively), and thus a population of TCR Vβ genes will therefore show a "spectrum" of different CDR3 lengths.

Under normal circumstances, this spectrum is highly variable, showing multiple "peaks" (with varying heights as detected by the PCR reactions distributed in a Gaussian pattern), representing a polyclonal repertoire of T cells (i.e., different TCR variable chain families with different CDR3 lengths per individual family). Under pathologic conditions, skewing from polyclonal to oligoclonal, and in malignant conditions, monoclonal, can be detected by repertoire analysis. Specific patterns of immunodominant clonotypes can be discerned in immune-mediated diseases, including autoimmune disease, allogeneic responses (e.g., graft vs. host, rejection), bone marrow failure disorders (e.g., aplastic anemia) and in reaction to foreign antigens (infections), in which this type of repertoire analysis may aid in vaccine development.

C. Mutation Analysis

1. **Sanger sequencing.** Direct detection of mutations in genomic DNA or reverse-transcribed mRNA (cDNA) by the chain-termination (Sanger) sequencing method is the cornerstone of genetic diagnosis. Sequencers are automated and capable of running up to 96 reactions, each with all four dideoxynucleotides per reaction. However, this still involves significant labor and reagent cost for each sample preparation as well as substantial time for data analysis as there is no reliable software for automated mutation analysis at a clinical level. The basic technique involves the use of a mixture of normal (deoxy) and modified (dideoxy) nucleo-tides during a PCR. Each of the modified nucleotides is labeled with different fluorochromes and unable to support additional extension of the DNA chain, such that once incorporated into a growing chain, the reaction terminates. At the end of the sequencing PCR reaction, thousands of fragments of different lengths are generated, ranging from one base pair to the full length of the amplicon (typically in the 400 to 600 base pair [bp] range). Each of these fragments contains a labeled nucleotide in the last position, and evaluation depends on separating these fragments based on size using capillary electrophoresis inside the sequencing instrument. Once aligned by size, the fragments are excited by a light source (commonly a laser) and the "color" of the terminating nucleotide is identified, and these are assembled generating a graphic display called chromatogram or spherogram (Fig. 20-6).

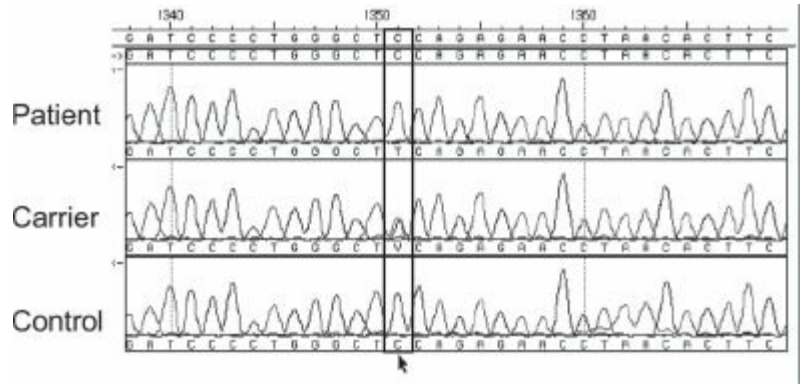

Figure 20-6. A single nucleotide substitution in the patient results in a defect (Xmutant [Xm]; top tracing) in the expression of the common gamma chain resulting in X-linked SCID. The maternal carrier has one normal allele and one mutant allele (X/Xm; middle tracing), and the female control has two normal alleles (X/X; bottom tracing).

DNA fragments from autosomes will generate chromatograms with single peaks for each base if both copies have the same sequence. However, if a single base pair mutation is present in one of the alleles, the chromatogram will display two peaks at that specific position, meaning that half the fragments in the reaction finished in one base and the other half in the alternative base. This characterizes a heterozygous mutation. In the case of a homozygous change, the mutant DNA will display only one base at the specific position, but that will be different from the reference sequence. In the case of sex chromosome mutations in males, the existence of one single X and Y chromosome implies that every mutation on these chromosomes will be displayed as single peaks in disagreement with the reference sequence (Fig. 20-6), similar to homozygous mutations. These mutations are called hemizygous. The maternal carrier for this mutation will demonstrate a heterozygous pattern with one normal and one mutant X chromosome detected (Fig. 20-6). Clearly, mutations that involve more than one base will generate a more complicated display pattern than single nucleotide substitutions.

Limitations of this technique include high cost per base sequenced, low throughput and inability to detect large structural or copy number variations, such as large deletions or insertions. It has also poor detection sensitivity for somatic mutations present at low frequency and mutations in areas not targeted, such as promoters or other regulatory regions found outside of the actual coding region, will not be detected.

2. **Next-generation sequencing techniques.** Given the high cost and low throughput of Sanger sequencing, alternative sequencing techniques have been developed. Major commercial entities include Illumina, Applied Biosystems, Roche/454, and Complete Genomics. These platforms have in common the capability to sequence from a few hundred thousand to several million DNA fragments in parallel, markedly increasing the throughput and decreasing the cost per base multifold when compared to Sanger sequencing.

   These technologies are used to sequence entire human genomes, cancer genomes, microbial genomes, epigenetics studies, and RNA sequencing and counting. Applying these tools to clinical setting has been slow due to the high instrument cost, exaggerated throughput (up to 300 billion bases per run, currently), short read lengths, together with associated massive data storage, and analysis challenges. More recent instruments aimed at clinical laboratories have lower throughputs, from 10 Mb to 1 Gb per run, lower cost per

run (from $500.00 to $1000.00), and longer read lengths, ideal for amplicon sequencing. These instruments are changing the clinical genetics field, though substantial hurdles still need to be overcome including the development of user-friendly automated data analysis software and sample preparation methods.

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21

Adverse Responses to Vaccines

John M. Kelso

Vaccination against infectious diseases constitutes one of medicine's greatest success stories, decreasing the incidence of, or in some cases completely eliminating, conditions that previously caused great morbidity and claimed tens of thousands of lives. Diseases such as diphtheria, *Haemophilus influenzae* type b, measles, mumps, poliomyelitis, rubella, smallpox, and tetanus have been virtually eliminated. The overwhelming majority of patients who are vaccinated suffer no, or only very minor, self-limited, reactions. On rare occasions, vaccinated individuals have more serious reactions and require evaluation. The goals of this evaluation are to determine the following: Was the reaction due to the vaccine? What was the nature of the reaction? What constituent of the vaccine was responsible? Can the patient receive the suspect or other vaccines again in the future? The answer to this last question is almost always yes because the risk posed by careful revaccination is almost always less than the benefit of being fully immunized against preventable diseases. The immunologic response to vaccination often produces some inflammation that may result in injection site reactions or mild systemic reactions such as fever. These common reactions do not contraindicate future doses of any vaccine. More serious reactions, both allergic and nonallergic, may occur but rarely contraindicate future doses.

APPROACH TO THE PATIENT WITH AN APPARENT ADVERSE RESPONSE TO A VACCINE

Critical to the evaluation of an apparent adverse response to a vaccine are the nature and timing of the reaction. Presumably, for a vaccine to be suspected of causing an adverse reaction, the reaction would have to be temporally associated with vaccination, although depending on the type of adverse reaction, it may occur minutes to days later. Hypersensitivity (immunologically mediated) reactions related to vaccine constituents can be immediate or delayed and are more often due to an excipient rather than the immunizing agent itself. The pathophysiology of other adverse reactions is less clear and may or may not be immunologically mediated. For reactions whose nature and timing are consistent with an IgE-mediated mechanism, skin testing with the vaccine and vaccine constituents is appropriate to try to confirm that IgE antibodies are responsible and determine to what vaccine component they are directed. This information guides the approach to subsequent vaccination with the suspect vaccine or any other vaccine with a common allergenic ingredient. Allergy to a vaccine or vaccine ingredient does not contraindicate future vaccination, but rather warrants determination of the necessity of such future vaccination and development of an approach to future vaccination that minimizes risk (Fig. 21-1).

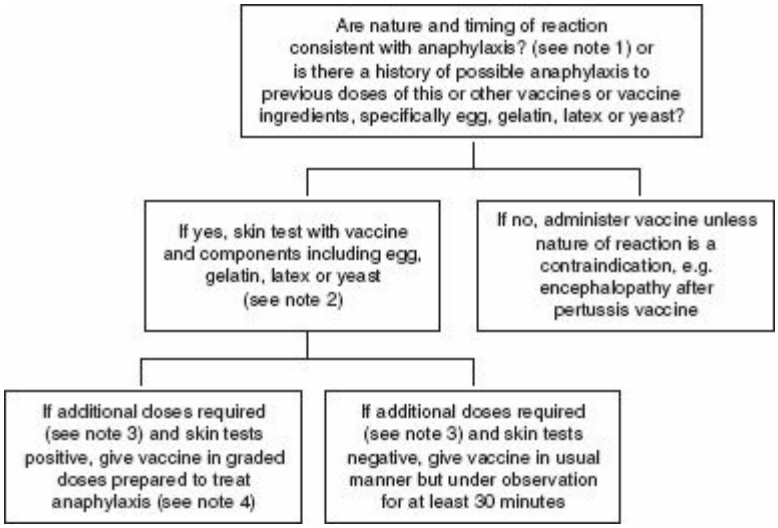

Figure 21-1. Suggested approach to suspected adverse reactions to a vaccine.

Note 1. Are nature and timing of reaction consistent with anaphylaxis?

Probable Anaphylactic Reaction: reaction occurring within 4 hours of vaccine administration to include signs and/or symptoms from more than one of the following systems:

– Dermatologic: urticaria, flushing, angioedema, pruritus
– Respiratory: rhinoconjunctivitis (red, watery, itchy eyes; stuffy, runny, itchy nose; sneezing), upper airway edema (change in voice, difficulty swallowing, difficulty breathing), bronchospasm/asthma (cough, wheeze, shortness of breath, chest tightness)
– Cardiovascular: hypotension, tachycardia, palpitations, light-headedness, loss of consciousness (Note: Hypotension or loss of consciousness with pallor and bradycardia is much more likely a vasovagal reaction.)
– GI: cramping, nausea, vomiting, diarrhea

Possible Anaphylactic Reaction:

Signs and/or symptoms from only one system (as above)

Signs and/or symptoms from more than one system (as above) but occurring more than 4 hours after vaccination

Note 2. Skin tests with vaccine and components including egg, gelatin, latex, or yeast

Vaccine skin tests:

– Prick test with full-strength vaccine (consider dilution if history of life-threatening reaction).
– If prick test with full-strength vaccine negative, intradermal test with 0.02 mL vaccine 1:100
– Note: Vaccine skin tests may cause false (or clinically irrelevant) positive reactions.

Vaccine ingredient skin tests/*in vitro* tests:

– Prick tests with commercial extracts of egg (influenza and yellow fever vaccines) or *S. cerevisiae* yeast (hepatitis B vaccine and quadrivalent human papillomavirus vaccine). – Prick test with sugared gelatin (e.g., Jell-O®: dissolve 1 teaspoon (5 g) of gelatin powder in 5 mL normal saline) or *in vitro* assay for specific IgE antibody. Vaccines that contain gelatin: influenza (some brands), measles, mumps, rabies (some brands), rubella, varicella, yellow fever, zoster – Prick test with latex (soak two fingers of latex glove or a toy balloon in 5 mL normal saline) or *in vitro* assay for specific IgE antibody. Vaccines that contain latex in packaging: http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/latex-table.pdf

Note 3. If fewer than the recommended number of doses received, consider measuring level of IgG antibodies to immunizing agent. If at a level associated with protection from disease, consider withholding additional doses, although magnitude and duration of immunity may be less than those if all doses were received.

Note 4. Vaccine administration in graded doses

For a vaccine where usual dose is 0.5 mL, administer graded doses of vaccine at 15-minute intervals: 0.05 mL of 1:10 dilution, 0.05 mL of full strength, 0.1 mL of full strength, 0.15 mL of full strength, 0.2 mL of full strength. For influenza vaccine in egg-allergic patients, administer as a single dose and observe for 30 minutes.

I. PRIOR KNOWN ALLERGY TO A VACCINE CONSTITUENT

Some patients have a history of apparent allergic reactions to substances that are contained in vaccines, as opposed to a history of reacting to the vaccine itself. If a person has reacted to a vaccine itself, it must be assumed that some constituent of the vaccine is present in a large enough quantity to have caused the reaction. However, if a person has reacted to a substance also contained in a vaccine, for example, an allergic reaction to the ingestion of eggs, the amount of this substance in the vaccine may not be enough to cause an allergic reaction to vaccination. The reverse is also true, that is, that patients may report no reaction to a substance also contained in a vaccine, for example, denying any reaction to the ingestion of eggs, yet still react to the substance in the vaccine because it is in a different form (e.g., unheated) or different route of exposure (e.g., parenteral). Thus, while it is appropriate to screen for reported allergies to vaccine components such as egg, gelatin, yeast, or latex prior to vaccine administration, such screening will identify some patients who may tolerate vaccination despite their allergy and will not identify all patients who will react to those substances in vaccines.

A. Immediate-type, IgE-mediated reactions

As with most immediate-type, IgE-mediated allergic reactions, the allergens are usually proteins. The proteins most often implicated in vaccine reactions are egg and gelatin, with perhaps rare reactions to yeast or latex.

1. Egg

Measles and mumps vaccines, as well as one type of rabies vaccine, are grown in chick embryo fibroblast cell cultures and do not contain egg proteins in sufficient quantities to pose a risk to egg-allergic individuals. These vaccines can be administered without special precautions even to patients with histories of severe reactions to the ingestion of eggs.

Only two vaccines, influenza (both injectable inactivated and nasal live attenuated) and yellow fever, are grown in chicken eggs and thus contain residual egg protein in sufficient amounts to possibly constitute a risk when vaccinating egg-allergic recipients.

Although influenza vaccine skin testing has been used to try to predict whether or not egg-allergic patients who are to receive the vaccine will have an allergic reaction, studies have indicated that most egg- allergic patients, even with positive vaccine skin test results, tolerate the vaccine uneventfully. Further, influenza vaccines in recent years contain very low amounts of egg protein. Nonetheless, patients who are suspected of being allergic to eggs should be evaluated by an aller-gist/immunologist prior to receiving influenza

vaccine. This evaluation should confirm by history and skin testing or *in vitro* testing that the patient is still allergic to eggs, since this allergy is often outgrown. If the patient is still egg-allergic, it is appropriate to choose an age-appropriate influenza vaccine. The vaccine should be administered under observation for 30 minutes, and the health care provider should be prepared to treat a systemic allergic reaction should it occur.

Yellow fever vaccine contains a larger amount of egg protein than influenza vaccines, and there are fewer reports on administering the vaccine to egg-allergic patients. The package insert for the vaccine describes a protocol involving skin testing the patient with the vaccine and, if positive, giving the vaccine in graded doses as follows: Prick skin test with the vaccine diluted 1:10 in normal saline with positive (histamine) and negative (saline) control tests. If negative, intradermal skin test with the vaccine diluted 1:100 and controls. If the skin tests are negative, the vaccine can be administered as a single dose under observation. If the skin tests are positive, the vaccine can be administered in graded doses, subcutaneously at 15-minute intervals: 0.05 mL of 1:10 dilution, 0.05 mL of full strength, 0.1 mL of full strength, 0.15 mL of full strength, and 0.2 mL of full strength. Although this procedure is described as a "desensitization," it would need to be repeated for subsequent doses of the vaccine should they be required.

2. Gelatin

Measles/mumps/rubella (MMR), varicella, yellow fever, zoster, and some brands of influenza and rabies vaccines, contain gelatin as a stabilizer (Table 21-1). People with a history of food allergy to gelatin may develop anaphylaxis after receipt of gelatin-containing vaccines. Such patients should be evaluated by an allergist/immunologist prior to receiving such vaccines. There are no FDA-approved, commercially available skin test reagents for gelatin, but a crude extract for prick testing can be made by dissolving 1 teaspoon (~5 g) of any flavor of sugared gelatin (e.g., Jell-O®) powder in 5 mL normal saline (unfla-vored, unsugared gelatin tends to gel at room temperature). There are commercially available *in vitro* tests for specific IgE antibodies ("RAST") to both bovine and porcine gelatin, which are extensively cross-reactive. If the history and skin or *in vitro* tests confirm the gelatin allergy, alternate vaccines without gelatin should be administered when available. This however only applies to influenza and rabies vaccines where there are brands that do not contain gelatin. All of the other gelatin-containing vaccines do not have non–gelatin-containing alternative brands available. If the patient needs the vaccine, consideration can be given to administering the vaccine in graded doses (Fig. 21-1) under observation, prepared to treat anaphylaxis.

Table 21-1 Gelatin Content of Vaccines

Vaccine	Gelatin Content
Influenza (Fluzone, Sanofi Pasteur)	250 µg per 0.5 mL dose
Influenza (FluMist, MedImmune Vaccines)	2,000 µg per 0.2 mL dose
Measles, Mumps, Rubella (ATTENUVAX, MERUVAXII, MMRII, MUMPSVAX, Merck)	14,500 µg per 0.5 mL dose
Measles, Mumps, Rubella, Varicella (ProQuad, Merck)	11,000 µg per 0.5 mL dose
Rabies (RabAvert, Novartis)	12,000 µg per 1.0 mL dose
Typhoid Vaccine Live Oral Ty21a (Vivotif, Crucell)	Capsule
Varicella (VARIVAX, Merck)	12,500 µg per 0.5 mL dose
Yellow Fever (YF-VAX, Sanofi Pasteur)	7,500 µg per 0.5 mL dose
Zoster (ZOSTAVAX, Merck)	15,580 µg per 0.65 mL dose

Note: Subject to change—check package insert.

3. Latex

Dry natural rubber latex is used in packaging, that is, vial stoppers and syringe plungers, for some vaccines. The rubber used in packaging for some other vaccines is synthetic and poses no risk to the latex-allergic patient. Information about latex used in vaccine packaging is available in the manufacturer's package inserts or at http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/latex-table.pdf.

Although most IgE-mediated, immediate-type allergic reactions to latex have occurred in association with dipped products such as medical gloves (natural rubber latex or NRL), studies have demonstrated that molded products such as vial stoppers and syringe plungers (dry natural rubber or DNR) can elute latex allergens after being in prolonged contact with a solution or through multiple punctures of vial stoppers. Hypersensitivity reactions to latex after immunizations are rare; however, latex-allergic patients should be evaluated by an allergist/ immunologist prior to receiving vaccines with latex in the packaging. There are no FDA-approved, commercially available skin test reagents for latex, but a crude extract for prick testing can be made by soaking powdered latex gloves or toy balloons in normal saline. There are commercially available *in vitro* tests for specific IgE antibodies ("RAST") to latex. If the history and skin or *in vitro* tests confirm the latex allergy, alternate vaccines without latex should be administered when available. It may also be useful to remove the latex stopper and draw up the vaccine directly. However, given how difficult it is to elute latex allergen out of vaccine packaging and how rare reports are of allergic reactions to latex in vaccine packaging, even if no non–latex-containing vaccine alternatives are available, consideration can certainly be given to administering the vaccine under observation, prepared to treat an allergic reaction should it occur.

4. Yeast

Hepatitis B and quadrivalent human papillomavirus vaccines are manufactured in brewer's or baker's yeast (*Saccharomyces cerevisiae*). In theory, vaccine recipients with hypersensitivity to yeast could experience an allergic reaction to these vaccines. However, allergy to yeast is exceedingly rare. Patients claiming such an allergy should be evaluated by an

allergist/immunologist prior to receiving yeast-containing vaccines. There are commercially available skin test reagents as well as *in vitro* tests for specific IgE antibodies ("RAST") to *S. cerevisiae*. In the rare patient with a history of allergy to yeast and a positive skin or *in vitro* test, consideration can be given to administering the vaccine in graded doses under observation, prepared to treat an allergic reaction should it occur.

B. Delayed-type, cell-mediated reactions

As with most delayed-type, cell-mediated allergic reactions, the allergens are usually small molecules. The small molecules present in vaccines include thimerosal, aluminum, and antimicrobials.

1. Thimerosal

Most patients with delayed-type hypersensitivity reactions (allergic contact dermatitis) to thimerosal tolerate the injection of vaccines containing thimerosal uneventfully or with only temporary swelling at the injection site. This is not a contraindication to receiving vaccines that contain thimerosal.

2. Aluminum

Persistent nodules have occurred at the site of injection of aluminum (alum)-containing vaccines, likely as a result of delayed-type hypersensitivity to this vaccine adjuvant. In some cases, these reactions may be caused by the vaccine being inadvertently administered subcutaneously rather than intramuscularly. Only if such reactions were severe would they constitute a contraindication to further vaccination with aluminum-containing vaccines.

3. Antibiotics

No vaccine currently licensed for use in the United States contains penicillin. Many vaccines contain trace amounts of streptomycin, neomycin, and/or polymyxin B. Some people have delayed-type allergy to these agents and may develop an injection site nodule after vaccine administration. This is not a contraindication to future doses of vaccines containing these agents. However, if a patient has a history of an anaphylactic reaction to one of these antibiotics (exceedingly rare), he or she should be evaluated by an allergist/ immunologist prior to receiving vaccines containing them.

II. VACCINE CONTRAINDICATIONS BASED ON UNDERLYING MEDICAL CONDITION

In addition to prior reactions to vaccines or vaccine constituents, there are some underlying medical conditions, such as pregnancy and immune compromise, that may contraindicate vaccine administration because the condition might predispose to an adverse outcome. Details and specific recommendations can be found at http://www.cdc.gov/vaccines/recs/vac-admin/downloads/contrain-dications-guide-508.pdf

A. Pregnancy

There is a theoretical risk of causing disease in the fetus by administering a live vaccine to a pregnant woman, although smallpox is the only vaccine known to have done so. Nonetheless, pregnant women should not receive any live vaccines (Table 21-2). Human papillomavirus vaccine (HPV) should also not be administered during pregnancy because

it has not been studied. Inactivated (injectable) influenza vaccine is specifically indicated in pregnancy, and other vaccines such as tetanus (Td or Tdap) and hepatitis B should be administered in pregnancy if otherwise indicated.

Table 21-2 Live versus Killed Vaccines

Live Vaccines	Killed Vaccines
Bacille Calmette–Guerin (BCG)	Diphtheria, tetanus, acellular pertussis (DTaP, Tdap)
Influenza (intranasal)	Diphtheria–tetanus (DT, Td)
Measles–mumps–rubella (MMR)	Hepatitis A
Oral poliovirus (OPV)	Hepatitis B
Rotavirus	Hib conjugates
Typhoid (oral)	Human papillomavirus (HPV)
Vaccinia (smallpox)	Inactivated poliovirus (IPV)
Varicella	Influenza (injectable)
Yellow fever	Japanese encephalitis
Zoster	Meningococcal
	Meningococcal conjugate
	Pneumococcal
	Pneumococcal conjugate
	Rabies
	Typhoid (injectable)

B. Immune compromise

Generally, persons who are immunocompromised should not receive live vaccines (Table 21-2). Such vaccines rely on replication to stimulate an immune response, but because they are attenuated, this replication cannot lead to systemic disease in immunocompetent individuals. However, in immunocompromised persons, this replication, even of an attenuated microbe, can lead to systemic disease. There are important exceptions to this general rule, depending on the level of immune compromise and the risk of disease in specific populations. There is also a question of the effectiveness of live or killed vaccines in persons unable to mount an adequate immune response. Nonetheless, certain vaccines are specifically indicated in persons with immune compromise because their condition also places them at increased risk for infectious diseases that may be vaccine-preventable (Tables 21-3 and 21-4).

Table 21-3 Vaccination of Persons with Primary Immune Deficiencies

Category	Specific Immunodeficiency	Contraindicated Vaccines[a]	Recommended Vaccines[a]	Effectiveness and Comments
B-lymphocyte (humoral)	Severe antibody deficiencies (e.g., X-linked agammaglobulinemia and common variable immunodeficiency)	OPV[b] Small LAIV BCG Ty21a (live oral typhoid) Yellow fever	Pneumococcal Consider measles and vanicella vaccination	The effectiveness of any vaccine is uncertain if it depends only on the humoral response (e.g., PPSV or MPSV4). IGIV interferes with the immune response to measles vaccine and possibly vanicella vaccine.
	Less severe antibody deficiencies (e.g., selective IgA deficiency and IgG subclass deficiency)	OPV[b] BCG Yellow fever Other live vaccines appear to be safe.	Pneumococcal	All vaccines likely effective. Immune response might be attenuated.
T-lymphocyte (cell-mediated and humoral)	Complete defects (e.g., severe combined immunodeficiency [SCID] disease, complete DiGeorge syndrome)	All live vaccines[c,d,e]	Pneumococcal	Vaccines may be ineffective.
	Partial defects (e.g., most patients with DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia-telangiectasia)	All live vaccines[c,d,e]	Pneumococcal Meningococcal Hib (if not administered in infancy)	Effectivenss of any vaccine depends on degree of immune suppression.
Complement	Persistent complement, properdin, or factor B deficiency	None	Pneumoccoccal Meningococcal	All routine vaccines likely effective.
Phagocytic function	Chronic granulomatous disease, leukocyte adhesion defect, and myeloperoxidase deficiency.	Live bacterial vaccines[c]	Pneumococcal[f]	All inactivated vaccines safe and likely effective. Live viral vaccines likely safe and effective.

[a] Other vaccines that are universally or routinely recommended should be given if not contraindicated.

[b] OPV is no longer available in the United States.

[c] Live bacterial vaccines: BCG, and Ty21a *Salmonella typhi* vaccine.

[d] Live viral vaccines: MMR, MMRV, OPV, LAIV, yellow fever, vanicella, zoster, rotavirus, zoster, rotavirus, and vaccinia (smallpox). Smallpox vaccine is not recommended for children or the general public.

[e] Regarding T-lymphocyte immunodeficiency as a contraindication for rotavirus vaccine, data exist only for severe combined immunodeficiency.

[f] Pneumococcal vaccine is not indicated for children with chronic granulomatous disease beyond age-based universal recommendations for PCV. Children with chronic granulomatous disease are not at increased risk for pneumococcal disease. (From Centers for Disease Control and Prevention. General recommendations on immunization—recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2011;60(2):1–64.)

Table 21-4 Vaccination of Persons with Secondary Immune Deficiencies

Specific Immunodeficiency	Contraindicated Vaccines[a]	Risk-Specific Recommended Vaccines[a]	Effectiveness and Comments
HIV/AIDS	OPV[b] Smallpox BCG LAIV Withhold MMR and varicella in severely immunocompromised persons. Yellow fever vaccine might have a contraindication or a precaution depending on clinical parameters of immune function.[c]	Pneumococcal Consider Hib (if not administered in infancy) and Meningococcal vaccination.	MMR, varicella, rotavirus, and all inactivated vaccines, including inactivated influenza, might be effective.[d]
Malignant neoplasm, transplantation, immunosuppressive or radiation therapy	Live viral and bacterial, depending on immune status.[e,f]	Pneumococcal	Effectiveness of any vaccine depends on degree of immune suppression.
Asplenia	None	Pneumococcal Meningococcal Hib (if not administered in infancy)	All routine vaccines likely effective.
Chronic renal disease	LAIV	Pneumococcal Hepatitis B[g]	All routine vaccines likely effective.

[a] Other vaccines that are universally or routinely recommended should be given if not contraindicated.

[b] OPV is no longer available in the United States.

[c] Symptomatic HIV infection or $CD4^+$ T-lymphocyle count of <200/mm^3 or <l5% of total lymphocytes for children <6 y of age is a contraindication to yellow fever. vaccine administration. Asymptomatic HIV infection with $CD4^+$ T-lymphocyte count of 200–499/mm^3 for persons ≥6 y of age or 15%–24% of total lymphocytes for children <6 y of age is a precaution for yellow fever vaccine administration. Details of yellow fever vaccine recommendations are available from CDC. (CDC. Yellow Fever Vaccine: Recommendations of the ACIP. *MMWR* 2010:59 [No RR-7].)

[d] HIV-infected children should receive IG after exposure to measles, and may receive varicella, measles, and yellow fever vaccine if $CD4^+$ T-lymphocyte count is ≥15%.

[e] Live bacterial vaccines: BCG, and Ty21a *Salmonella typhi* vaccine.

[f] Live viral vaccines: MMR, MMRV, OPV, LAIV, yellow fever, varicella, zoster, rotavirus, and vaccinia (smallpox). Smallpox vaccine is not recommended for children or the general public.

[g] Indicated based on the risk from dialysis-based bloodborne transmission.

(From Centers for Disease Control and Prevention. General recommendations on immunization— recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2011;60(2): 1–64.)

C. Asthma

Live attenuated influenza vaccine (LAIV) should not be given to patients with asthma because it may cause an asthma exacerbation.

III. OTHER VACCINE REACTIONS REQUIRING EVALUATION PRIOR TO SUBSEQUENT VACCINATION

A. Encephalopathy

Encephalopathy is a severe neurologic reaction rarely associated with pertussis-containing vaccines (DTaP or Tdap) and is an absolute contraindication to subsequent administration of such vaccines. Instead, DT or Td should be used for subsequent vaccination. Lesser reactions to pertussis-containing vaccines, such as febrile seizures, hypotonic episodes, or inconsolable crying, are not contraindications to future doses.

B. Guillain-Barré Syndrome (GBS)

Cases of GBS have been reported in temporal association with influenza and other vaccines. The rate of these reactions is so low that it cannot be determined if the relationship is causal or coincidental. If a patient has a history of GBS within 6 weeks of receipt of a vaccine, subsequent dose of the vaccine should be withheld due to a risk of recurrence unless the patient is at particularly high risk of the disease.

IV. CONTROVERSIES REGARDING VACCINE ADMINISTRATION

A number of controversies have arisen in regard to potential long-term adverse consequences of vaccination. A case series of 12 children published in the late 1990s claimed an association between MMR vaccination and autism. Subsequent large, well-designed, carefully conducted epidemiologic studies universally have found no such association. Also in the late 1990s, concern was raised about exposure to thimerosal, which was used as a preservative in many vaccines, because thimerosal is 50% mercury by weight and mercury is neurotoxic. It has been removed from childhood vaccines, although no reports, before or since, actually demonstrated any adverse outcome of this exposure. A number of other associations between vaccination and diseases such as multiple sclerosis and atopic diseases have been claimed, but again subsequent more robust scientific evaluations have not substantiated these associations.

V. IMMUNIZATION SCHEDULES

Current immunization schedules for children, adolescents, and adults can be found at http://www.cdc.gov/vaccines/recs/schedules/default.htm.

SUGGESTED READINGS

CDC Vaccines & Immunizations. www.cdc.gov/vaccines

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22

Complementary Medicine in Allergy and Immunology

Timothy Ryan Mainardi and Leonard Bielory

OVERVIEW

Complementary and alternative medicine (CAM) therapies such as Traditional Chinese Medicine (TCM), Ayurvedic (traditional Indian) medicine, acupuncture, yoga, homeopathy, chiropractic medicine, and massage therapy are gaining widespread popularity in the United States and throughout the world for the treatment of asthma and allergies due to their reputed effectiveness, low cost, and favorable safety profiles. CAM is commonly defined as a group of diverse medical and health care systems, practices, and products that are not generally considered part of the conventional allopathic medical practices. Complementary medicine commonly reflects "in addition to" rather than "a substitute for" clinical interventions, whereas "alternative medicine" refers to therapies used in place of traditional medicine.

Patients are often interested in CAM for chronic conditions either because conventional therapies are unsatisfactory or because of concerns about side effects of synthetic drugs. The increasing prevalence and chronic nature of allergic diseases and lack of preventive and curative therapy influence allergy and asthma patients in Western societies to sometimes seek CAM remedies.

In most Western countries, the dichotomy between CAM and the dominant medical therapeutic culture leads to difficulties integrating the best therapeutic interventions based on "evidence-based approaches" with CAM, with the goal of guiding and optimizing patient health care outcomes. In the past, CAM interventions have been marginalized because allopathic medical health care providers who are educated in "pharmaceutical-based medicine" offer patients the most effective and scientifically validated form of medicine based on primary pharmaceutical interventions.

I. EPIDEMIOLOGY

A. Use in the United States

1. The use of CAM in the United States is increasing; in 1991, approximately 33.8% of the US adult population used at least 1 of 16 different types of CAM therapy ("prayer" included as CAM therapy), and by 1997, the usage had increased to 42.1% (83 million people). The typical users of CAM are college-educated white women, between the ages of 40 and 60. In 2007, 38% of adults and 12% of children had used CAM in the past year (not including "prayer," the most common CAM therapy) consisting of natural products (18%), deep breathing exercises (13%), meditation (10%), chiropractic or osteopathic manipulation (9%), massage (9%), and yoga (6%). Of those using natural products, Echinacea (20%), Ginkgo biloba (14%), and combination herbal pills (13%) were the most commonly used.

B. Why Patients May Use CAM

1. Chronic unrelenting diseases where CAM is often employed include musculoskeletal disorders, asthma, allergies, and immunodeficiencies. CAM interventions for the treatment of allergic disorders concentrate on herbal remedies derived from medicinal plants, homeopathy, acupuncture, and Ayurvedic interventions.

C. Patient Populations Likely to Use CAM

1. Use of CAM, especially natural products for chronic diseases, is nothing new. In the 1940s and 1950s, pharmacists sold a product known as "Asthmador," which contained belladonna, an anticholinergic-containing herb. Ma huang was commonly used in herbal preparations marketed for use in asthma, until the FDA banned sales of ephedra-containing products in 2003. Patients most likely to use CAM in the United States and Europe are middle-class (economically) adults between the ages of 30 and 69, women more likely than men, and those more likely to hold graduate degrees (55%) when compared with those with less than high school education (21%). The most important patient information sources regarding CAM include current medical practitioner (40%) or friends and family (37%). Of note, much of the cost of CAM in Europe is paid for in part or in total by the public health insurance system, while in the United States, it is primarily paid "out of pocket" by the patient.

II. CATEGORIES OF CAM

A. Acupuncture

1. Acupuncture is a cornerstone of the **Traditional Chinese Medicine (TCM)** system. It is widely used to treat many chronic illnesses, including asthma, depression, and arthritis. Acupuncture is used by practitioners to restore the balance of "vital flows" by inserting needles at exact points (acupoints) to stimulate specific subcutaneous sites of the body. **Well-controlled trials have demonstrated that acupuncture can be effective for the treatment of chronic migraines, nausea secondary to chemotherapy, and chronic lower back pain**. Although acupuncture is often used to treat allergic rhinitis, most studies investigating this treatment are of poor quality, not randomized, or not controlled. In a well-designed crossover, two-phase, single-blind, randomized trial of acupuncture versus sham acupuncture treatment for seasonal allergic rhinitis, a statistically significant reduction in the severity of nasal and nonnasal symptoms of allergic rhinitis in the acupuncture group was demonstrated, though the use of conventional antiallergic medications was not significantly different between groups. Another study similarly demonstrated acupuncture significantly decreased total nasal symptom scores and rhinorrhea, but not other symptoms, nor the use of relief medications. In a randomized, double-blind, sham-controlled study of pediatric patients with persistent allergic rhinitis, a statistically significant decrease in daily rhinitis score and more symptom-free days in the acupuncture treatment group were seen, while there was no significant difference between the groups for daily relief medication scores, blood eosinophil counts, serum IgE levels, and nasal eosinophil counts. There are also well-controlled studies that demonstrate no difference in clinical symptoms of allergic rhinitis between active and

control groups.

B. Homeopathy

1. Homeopathy is based on the belief that substances distinct from any disease-causing agent that can create symptoms similar to that specific disease can be used to cure the disease. This concept is known as the "**Law of Similars,**" and it was first used in the treatment of malaria when it was noted that the bark of the Cinchona tree caused fevers and rigors similar to the malaria it treated. True homeopathy requires "potentiation" of the substance through serial dilutions, which at times are so extensive as to make it mathematically impossible for the dilution to contain any of the actual substance.
2. Homeopathy in allergic diseases has been extensively studied through numerous rigorous trials conducted in allergic rhinitis. As a form of treatment for allergic diseases, homeopathy is quite popular. A retrospective (uncontrolled) study of people with hypersensitivity illnesses who choose treatment with general practitioners versus classical homeopaths found that those patients who sought care from homeopaths self-reported a significantly greater improvement in their overall health. One double-blind, placebo-controlled trial study of patients with allergic rhinitis showed a significant difference in favor of homeopathy, while another well-controlled study comparing cromolyn and an intranasal homeopathic remedy, *Luffa compositum Heel*, found no significant difference between the active and control groups. In several double-blind controlled studies in patients with seasonal or perennial allergic rhinitis, homeopathic treatments either have been shown to be marginally effective or demonstrated mixed efficacy, such as an effect in nasal flow measurements, but not necessarily in symptoms. Interestingly, in one randomized, double-blind trial, homeopathic preparations showed significantly better quality of life questionnaire scores compared to placebo. Although there is published literature suggesting that some beneficial effect of homeopathy exists, in many cases, this effect may be a placebo effect. An analysis of 100 clinical trials of homeopathy when compared to conventional allopathic medicine, matched for disease and outcome, concluded that the beneficial effects of homeopathy on allergic rhinitis were inconclusive and more rigorous studies are required.

C. Phytotherapy

1. Herbal preparations are becoming increasingly popular among patients looking for CAM therapies. Treatments based on herbs cannot all be considered as alternative or unconventional, as more than 60% of allopathic medications are derived from plants. However, in allopathic medicine, when an active and beneficial ingredient in an herb becomes isolated, its chemistry may be altered slightly to improve pharmaceutical characteristics or allow for patent protection; the pharmacokinetic and pharmacodynamic qualities are defined, and the absorption, distribution, metabolism, and elimination are characterized before a dose form for humans is created. This dose form leads to a reproducible blood level with defined and reproducible characteristics. Rarely is such precision possible in herbal preparations. Most herbal preparations are sold by weight of the parent herb, not the active ingredients, which can fluctuate widely depending on growing, harvesting, and storage conditions. This is an effect where, similar to the cultivation of wine, small differences in farming location and practice can have big effects

on the end product.

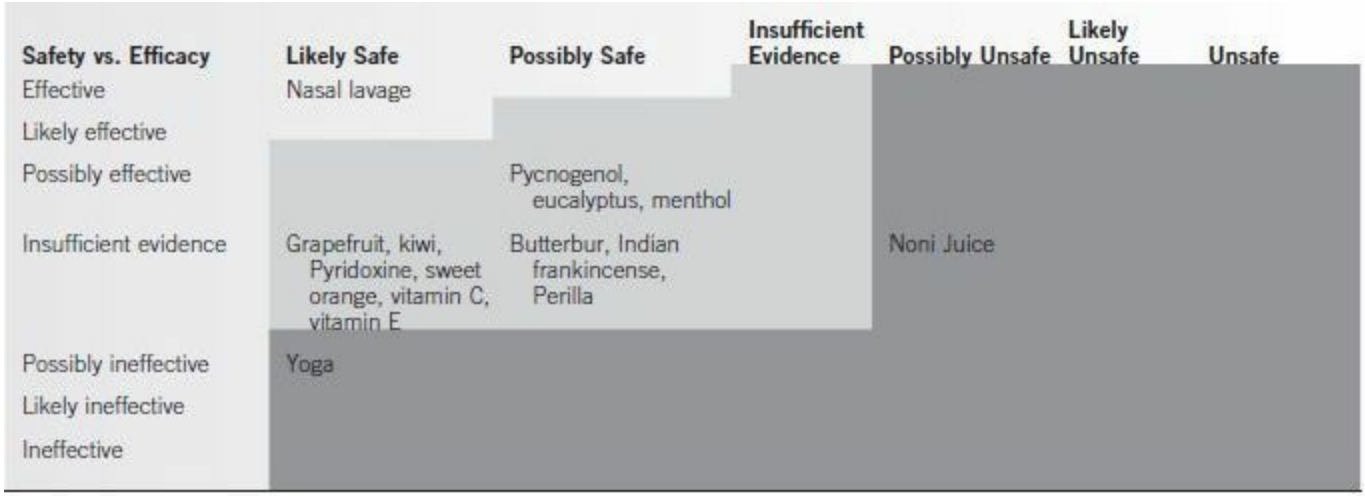
2. **Phytotherapy** can be divided into traditional and nontraditional herbal preparations. Traditional preparations from Chinese, Japanese, and Ayurvedic medicines often use groups of different herbs in fixed mixtures (i.e., *ma huang* and *saiboku-to*) to treat diseases including allergic rhinitis and asthma. Problems with herbal remedies can arise when hand-made mixtures are used or when herbs are used in combination with other CAM therapies. A trend seen in nontraditional herbal preparations involves using single herbs in fixed doses rather than mixtures of multiple herbs; examples include *Echinacea*, butterbur, and stinging nettle. Some physicians and nutrition centers are developing their own proprietary herbal mixes using both traditional and nontraditional data to create products that may or may not be reproducibly effective.
3. Phytotherapy: traditional therapies
    a. The literature on herbal remedies for allergic rhinitis is extensive because of the large variety of herbs and their combinations. Some of the most known and most commonly used herbs for allergic rhinitis and asthma are listed in Tables 22-1A and 22-1B. In general, the studies with herbal remedies are of low quality, but in many cases, a clinical effect can be measured in allergic rhinitis. A mixture of 18 traditional Chinese herbs, called **RCM-101**, shows significant differences in quality-of-life scores as well as its effect on various inflammatory mediators, such as decreased the production of prostaglandin E2 and nitrous oxide production in murine macrophages. In an animal model using rat peritoneal mast cells, RCM-101 inhibits the release and/or synthesis of histamine, leukotriene B4, and prostaglandin E2, which may account for some of its activity in allergic rhinitis.

Table 22-1A Selected Herb-derived Substances Used in the Treatment of Allergic Rhinitis

Safety vs. Efficacy	Likely Safe	Possibly Safe	Insufficient Evidence	Possibly Unsafe	Likely Unsafe	Unsafe
Effective	Nasal lavage					
Likely effective						
Possibly effective		Capsaicin, butterbur, quercetin			Ephedra	
Insufficient evidence	Echinacea, vitamin C	Tinospora, cordifolia Goldenseal, cat's claw, stinging nettle, spirulina		Bitter orange		
Possibly ineffective		Grape seed extract				
Likely ineffective						
Ineffective						

This assumes use of high-quality, uncontaminated products and the use of typical doses. Some products are never appropriate for specific patients due to concomitant disease states, potential drug interactions, or other clinical factors. Use good clinical judgment before recommending any product.

Table 22-1B Some Herb-derived Substances Used in the Treatment of Asthma



This assumes use of high-quality, uncontaminated products and the use of typical doses. Some products are never appropriate for specific patients due to concomitant disease states, potential drug interactions, or other clinical factors. Use good clinical judgment before recommending any product.

i. **Biminne,** is composed of 11 Chinese herbs and was used in trial of perennial allergic rhinitis patients. Use of Biminne showed a trend toward improvement over time in mean weekly symptom scores and physician overall evaluation; however, only sneezing was significantly reduced, and there was no effect on nasal obstruction.

ii. Anti-asthma simplified herbal medicine intervention (**ASHMI)** and Food allergy herbal formula (**FAFH-2)** are two preparations based on TCM. ASHMI is a mixture of three herbs (*Ganoderma lucida*, *Glycyrrhiza uralensis*, and *Sophorae flavescentis*), which are common herbs used in China for patients with asthma. A randomized clinical trial comparing prednisone to ASHMI in 91 moderate to severe asthmatics showed no significant symptom or β-agonist use difference between the groups; however, the prednisone group showed slight improvement in Peak expiratory flow (PEF) and force expiratory volume in one second (FEV_1). Food allergy herbal formula 2 (FAHF-2) and Food allergy herbal formula 1 (FAHF-1) are proprietary blends of herbs being studied for treatment of food anaphylaxis. Murine studies show that administration of FAFH-1 significantly attenuates anaphylaxis in mice previously sensitized to peanut.

4. Phytotherapy: nontraditional preparations

a. ***Urtica dioica*** **(stinging nettle)** is a common ingredient in homeopathic pharmacopeias for allergies. In a randomized controlled trial, *U. dioica* was superior to placebo for the treatment of allergic rhinitis. When combined with acupuncture, a Chinese herbal mixture similarly showed significant improvement in symptoms and quality of life scores, but the herbal treatment and acupuncture were not studied alone; therefore, no conclusions can be drawn about the efficacy of the individual components. A double-blind randomized, placebo-controlled trial showed that **grape seed** extract was no more effective than placebo in patients with ragweed-induced allergic rhinitis.

b. Because the mechanisms of action of most herbal treatments are unknown, there is the potential for herb–drug interactions if traditional and conventional medicines are used simultaneously. For example, **glycyrrhizin**, a Chinese herbal remedy for allergic rhinitis, interacts with angiotensin-converting enzyme inhibitors and is associated with

pseu-doaldosteronism (metabolic alkalosis and severe hypokalemia). **Reverse herbology**, which examines the effect of the herb or herbal mixture on the cytochrome P450 (CYP) enzymes and thus potential herb–drug interactions, demonstrates that sho-seiryu-to, a traditional mixture of eight herbs used to treat allergic rhinitis in Japan, has minimal effect on the CYP enzymes, xanthine oxidase, or *N*-acetyltransferase.

c. The potential mechanisms through which herbal medicines might affect allergic rhinitis have been studied. *Lycopus lucidus* (rough bugle-weed) demonstrated inhibition of mast cell–derived immediate-type allergic reactions through downregulation of proinflammatory cyto-kines, including Nuclear factor kappa beta (NF-KB). ***Shu-Bi-Lin*****,** a traditional Chinese herbal formula consisting of six herbs, was tested in a guinea pig model of allergic rhinitis comparing it to an antihis-tamine and found decreased eosinophil infiltration and endothelial nitric oxide synthase (eNOS) activity, as well as decreased sneezing and nasal scratching in the treatment group when compared to untreated controls. The same herbal preparation was also found to inhibit the release of IL-4, Tumor necrosis factor alpha (TNF-alpha), and IL-6 from human mast cell lines.

d. Butterbur, *Petasites hybridus*, a perennial shrub found throughout Europe as well as parts of Asia and North America, shows mixed results when studied in allergic rhinitis. Butterbur root compounds, known as petasins, are used to treat a variety of conditions including back pain, asthma, topical wound healing, and allergic rhinitis. Compared to cetirizine, treatment with butterbur is equally effective in decreasing symptom scores and improving quality of life, and both treatments are significantly better than placebo in decreasing symptoms of allergic rhinitis. Fexofenadine and butterbur were equivalent in decreasing symptom scores of allergic rhinitis patients; however, in a rigorous double-blind, placebo controlled, crossover study in patients with intermittent rhinitis, there was no significant effect of butter-bur on symptoms and nasal inspiratory peak flow. In uncontrolled postmarketing surveillance, 90% of patients self-reported improved seasonal allergic rhinitis symptoms while on butterbur treatment. The initial enthusiasm for butterbur was tempered, however, by the discovery that unprocessed butterbur extracts contained high levels of pyrrolizidine alkaloids, which are hepatotoxic and carcinogenic. Many commercially available preparations of butterbur have had the pyrrolizidine alkaloids removed.

e. ***Arthrospira platensis*** is an oxygenic, photosynthetic bacterium found in both fresh and salt water. **Spirulina, which** refers to the dried biomass of *A. platensis* used as a high-protein food throughout the world, inhibits histamine release from mast cells and exhibits some anti-inflammatory properties such as increased interferon-γ production and natural killer cell activity. In a randomized, double-blind, placebo-controlled trial, the spirulina group significantly reduced IL-4 levels. There are no large scale, controlled trials of spirulina in patients with allergic rhinitis.

D. Overview of Herbs

1. The traditional uses of herbal medicines are for the prevention and treatment of a variety of self-limiting to life-threatening illnesses, and herbal medicines are the most commonly consumed health care products. Scientific evaluation of herbal products is limited, but due

to inherent toxicity of many herbal remedies and because nearly all these remedies contain multiple, biologically active constituents, herb–drug interactions are a concern. Clinicians need to be aware of which herbs can cause toxicity and to be cognizant of potential herb–drug interactions. In many countries, herbal medicines are poorly regulated, may be neither registered nor controlled, and are rarely monitored by national surveillance systems for adverse events. However, the increasing popularity of herbal medicines raises concerns over their safety, quality, and efficacy on the part of health authorities and the general public. In response to these concerns, the World Health Organization publishes formal monographs on selected medicinal plants to establish quality standards of herbal products and outline the parameters for their safe and effective use. These monographs are highly correlated with the special expert committee of the German Federal Institute for Drugs and Medical Devices known as the Commission E monographs and ESCOP (European Scientific Cooperative on Phytotherapy) (http://www.escop.com/).

2. Drug interactions

a. Many of the constituents of herbal remedies compete with allopathic drugs for cytochrome P450 metabolism. Therefore drug interactions are a primary concern when patients are using herbal formulations.

3. Herbals having antiallergic effects

a. Natural medicines with antihistamine effects include **grape seed extract** (*Vitis vinifera*), B (*Pinus pinaster*) and B; those with deconges-tant potential include **bitter orange** (*Citrus aurantium*) and **ephedra** (*Ephedra* spp.); those with mast cell–stabilizing effects include **Indian frankincense** (*Boswellia serrata*), **picrorhiza** (*Picrorhiza kurroa*), **quercetin**, **spirulina**, and **stinging nettle** (*U. dioica*); those with leukotriene modifier effects include **butterbur** (*P. hybridus*), **fish oil, Indian frankincense** (*B. serrata*), **New Zealand green-lipped mussel** (*Perna canaliculus*), **perilla** (*Perilla frutescens*), and **pycnogenol** (*P. pinaster*). Natural antioxidants include grapefruit (*Citris para-disi*), kiwi (*Actinidia chinensis*), noni juice (*Morinda citrifolia*), sweet orange (*Citrus sinensis*), vitamin C, and vitamin E. Other agents with reported effects on allergies with various mechanisms not listed above include choline, eucalyptus (*Eucalyptus globulus*), magnesium, pyri-doxine (vitamin B6), soy (Glycine max), capsaicin, cat's claw (*Uncaria guianensis*, *Uncaria tomentosa*), goldenseal (*Hydrastis canadensis*), methylsulfonylmethane (MSM), and nasal irrigation.

4. Herbal Agents. The agents listed below are provided by their English, Latin, and pharmacopeial names followed by their common uses (not necessarily approved by any health authorities), contraindications, drug interactions and assorted reactions (allergic and idiosyncratic) (C = Common; R = Rare; U = Unlikely).

a. Garlic (*Allium sativum*) Bulbus Allii Sativi

i. **Common uses:** for cardiovascular health (hypertension, cholesterol and lipid lowering, atherosclerosis), relief of cough, cold symptoms, and rhinitis

ii. **Adverse effects:** gastrointestinal disturbances (C), hypoglycemia (R), change in body odor through the sweat and breath (C), and allergic reactions (R)

iii. **Contraindicated** in patients undergoing surgery since it can prolong bleeding time iv.

Drug interactions: increasing the anticoagulant effects of warfarin (C), bleeding times have been noted to be double in patients on warfarin and garlic supplements; changes pharmacokinetic variables of paracetamol (R); produces hypoglycemia when taken with chlor-propamide (R); may cause large increases in the minimum inhibitory concentration (MIC) to ampicillin over baseline values (R)

v. **Contraindications:** none known

b. Angelica (*Angelica archangelica*) Radix *Angelicae Sinensis*

i. **Common uses:** as an expectorant for bronchial illnesses, colds, and coughs; treatment of mild spasms of gastrointestinal tract, loss of appetite (anorexia nervosa), flatulence, and feeling of fullness; used in liqueurs such as Benedictine, Boonekamp, and Chartreuse

ii. **Adverse effects:** skin sensitization to sunlight due to the fura-nocoumarins causing photodermatitis and phototoxicity (R). Prolonged sunbathing and exposure to intense UV radiation must be avoided. Bleeding can occur when used with other anticoagulants (U).

iii. **Drug interactions:** none known

iv. **Contraindications:** use during pregnancy

c. Chamomile flower, German (*Chamomilla recutita, Matricaria recutita*) Flos Chamomillae

i. Name originates from the low-lying (chamos—ground) flower that has an apple scent (melos—apple).

ii. **Common uses:** for gastrointestinal inflammatory disorders, peptic ulcers, and spasms; topical cutaneous inflammation and bacterial infections; oral, throat, and mouth mucosal irritation; inhalations for the respiratory tract; baths for anogenital inflammation

iii. **Adverse effects:** exacerbation of allergic symptoms in ragweed-sensitive patients who have cross-reactivity with hazelnut, kiwi, birch, several Compositae (*Ambrosia*, *Chrysanthemum*, *Matricaria*, *Solidago*), and grass allergens (oral allergy syndrome primarily) (C); contact dermatitis (R); and anaphylaxis (R)

iv. **Drug interactions:** none known

v. **Contraindications:** none known

d. Black cohosh (root) (*Cimicifuga racemosa*) Cimicifugae racemo-sae rhizome

i. Used for premenstrual discomfort or menopausal symptoms

ii. Use during pregnancy is, in theory, contraindicated but has been used during first trimester to decrease uterine spasms; not to be given to children or during lactation

iii. **Drug interactions:** increases the action of antihypertensives; interacts with other hormone replacement therapies

e. Echinacea herb and root (*Echinacea angustifolia/Pallida/ Purpurea*) Herba/Radix *E. angustifolia/Pallida/Purpurea*

i. **Common uses:** At one time, the most common alternative herbal treatment, now is used by itself or in preparations for the common cold, flu-like illness, sore throat, and Herpes simplex virus (HSV-1).

ii. **Adverse effects:** Echinacea may cause increases in the MIC to ampicillin. Can cause

allergic reactions, exacerbation of asthma, and anaphylactic reactions.

iii. **Drug interactions:** No significant herb–drug interactions are known for Echinacea (*E. angustifolia*, *E. purpurea*, *E. pallida*); there is a potential risk of hepatotoxicity (R) and therefore this herb should not be used with other known hepatotoxic drugs, such as anabolic steroids, amiodarone, methotrexate, and ketoconazole.

iv. **Contraindications:** Although no specific contraindications are known, it is not recommended for use in patients with chronic systemic disease such as AIDS, tuberculosis, and other autoimmune disorders.

f. Ephedra (*Ephedra sinica*) Herba Ephedrae

i. **Common uses:** known as *ma huang*; used to treat asthma, bronchitis, and nasal congestion; as diet aids for weight loss; for enhancement of athletic performance; and for stimulation of the central nervous system due to its high content of ephedrine

ii. **Adverse effects:** hypertension (C), insomnia (C), tremor (C), heart palpitations (C), headache (C), nausea (C), loss of appetite (C), prostatism (C), cardiac arrhythmias (R), and even fatalities (R)

iii. **Drug interactions:** cardiac glycosides and halothane anesthetics, leading to arrhythmias (C); guanethidine enhances sympathomi-metic effect; Monoamine oxidase (MAO) inhibitors increase the sympathomimetic actions of ephedrine

iv. **Contraindications:** none known

g. Ginkgo (*Ginkgo biloba*) Folium Ginkgo

i. **Common uses:** for cerebral insufficiency, memory loss, concentration difficulties, fatigue, anxiety, headaches and depressed mood, peripheral arterial insufficiency, vertigo, and tinnitus

ii. **Adverse effects:** gastric or intestinal upsets (C), headaches (U), morbilliform (R), and other allergic skin reactions (R) due to sen-sitization to the ginkgolic acid

iii. **Drug interactions:** bleeding when combined with warfarin (U), elevated blood pressure when combined with a thiazide diuretic (U), and coma when combined with trazodone (R). Chronic use is associated with increased bleeding time (R) and spontaneous hemorrhage (R). Use with caution in patients receiving aspirin, Non-steroidal anti-inflammatory drugs (NSAIDs), anticoagulants, or other platelet inhibitors.

iv. Contraindications: none known

h. Licorice root (*Glycyrrhiza glabra*) Radix Glycyrrhizae

i. **Common uses:** Latin name derived from its common use as a sweetener (glukos—sweet) (riza—root) containing glycyrrhizin (or glycyrrhizinic acid) that is 50 times sweeter than sucrose. Used for treatment of gastric and duodenal ulcers, rhinoconjunctivi-tis, bronchitis, impaired digestion, bloating, and flatulence; as a demulcent for sore throats; as an anti-inflammatory in treating allergies and adrenocortical insufficiency.

ii. **Adverse effects:** Excessive ingestion (>20 g/d) produces excessive levels of aldosterone (pseudoaldosteronism) (U) resulting in headache (C), lethargy (C), sodium and water retention (C), hypertension (C), potassium loss (C), and myoglobinuria (R).

iii. **Drug interactions:** include agents that cause potassium loss, for example, thiazide diuretics; offsets the pharmacologic effect of spi-ronolactone; interferes with cardiac glycosides, for example, digoxin, pharmacodynamically

iv. **Contraindications:** in patients with cholestatic liver disorders, cirrhosis, hypokalemia, and renal insufficiency

i. St. John's wort (*Hypericum perforatum*) Herba Hyperici

i. Common uses: available in the United States as an alcoholic tincture, oral aqueous infusion, topical oil infusion, and dry capsules and tablets; in Germany, used as a tea (Hyperforat®), coated tablet (Jarsin®), juice (Kneipp®) and tincture (Psychotonin®), and in combination with valerian (Sedariston®). Used for neuralgia, anxiety, neurosis, micturition (Incontinuria®), and depression.

ii. **Adverse effects:** Photosensitization (R) can occur with 30 to 50 times the 900-mg recommended dose; a variety of other cutaneous eruptions.

iii. **Drug interactions:** lowers blood concentrations (C) of cyclosporin, amitriptyline, digoxin, warfarin, phenprocoumon, and the-ophylline; intermenstrual bleeding (U) when used concomitantly with oral contraceptives (ethinylestradiol/desogestrel); delirium when used with loperamide or mild serotonin syndrome (C) when used with amphetamines, MAO, or selective serotonin-reuptake inhibitors (sertraline, paroxetine, nefazodone, trazo-done, and other tricyclic antidepressants). Decreases antiretroviral action of indinavir (R). Increased sedation with paroxetine use

iv. **Contraindications:** none known

j. Peppermint oil and leaf (*Mentha piperitae*) Aetheroleum Menthae Piperitae and Folium Menthae Piperitae

i. Common uses: available as an oral and topical oil, inhalant, liniment, ointment, and tincture. Used for symptoms of indigestion, flatulence, irritable colon, and other gastrointestinal tract (spasmolytic) complaints, including those of the gallbladder and bile ducts. Also used for colds, rheumatic complaints, allergies, pruritus, urticaria, and pain in irritable skin conditions

ii. **Drug interactions:** no known drug interactions

iii. **Contraindications:** in patients with biliary obstruction, gallstones, and gallbladder inflammation (U); use on the face of infants and children due to risk of respiratory spasms (U)

k. Ginseng root (*Panax ginseng*) Radix Ginseng

i. **Common uses:** as an aphrodisiac and a stimulant

ii. **Adverse effects:** headache (U), tremulousness (U), and manic episodes (R) in patients treated with phenelzine sulfate. Chronic use associated with vaginal bleeding (R), mastalgia (R), mental status changes (R), and Stevens-Johnson syndrome (R).

iii. **Drug interactions:** interference with digoxin and hypoglycemic agents; lowers blood concentrations of alcohol and warfarin (R) and induces mania (R) if used concomitantly with phenelzine; possible additive effect on estrogens or corticosteroids (U)

iv. **Contraindications:** in patients with diabetes

l. Kava kava rhizome (root) (*Piper methysticum*) Piperis methystici rhizome

i. **Common uses:** for the short-term treatment for anxiety

ii. **Adverse effects:** severe hepatotoxicity including liver failure (R), dizziness (C), drowsiness (C), stomach upset (R), and allergic reactions (R)

iii. **Drug interactions:** potentiation of the sedative effect of anesthetics inducing a semicomatose state when given concomitantly with alprazolam (R); increasing "off" periods in Parkinson's patients taking levodopa (R)

iv. **Contraindications:** none known

m. Saw palmetto (berry) (*Serenoa repens*) Sabal fructus

i. **Common uses:** for urinary problems associated with benign prostatic hypertrophy

ii. **Adverse effects:** headache, nausea, vomiting, urinary retention (R), impotence (R), and hypersensitivity reactions (R)

iii. **Drug interactions:** anticoagulants (increased bleeding time) and from anti-inflammatory agents (aspirin and other nonsteroidal agents) (C); oral contraceptives (antiestrogen effect) (U)

iv. **Contraindications:** in pregnancy secondary to antiandrogenic properties, should be avoided during lactation or given to children

n. Stinging nettle root, herb, and leaf (*U. dioica*) Radix Urticae, herba/folium

i. **Common uses:** The Latin genus name comes from the term "burn" due to the urticate (stinging) nature of its hairs. Available as a freeze-dried powder, extract, and juice; or combined with saw palemetto (PRO®). Homeopathically used for the treatment of allergic rhinitis; natural product used for benign prostatic hypertrophy; for in general use for its anti-inflammatory effects in acute arthritis; as a diuretic

ii. **Drug interactions:** none known

iii. **Contraindications:** none known, although collection of fresh leaves can cause urticaria (C), burning and itching upon application to mucosal surfaces (C); is known to cause mild gastrointestinal disturbances and diarrhea (R)

o. Valerian root (*Valeriana officinalis*) Radix Valerianae

i. **Common uses:** for insomnia, restlessness, anxiety, and appetite stimulation

ii. **Adverse effects:** nephrotoxicity (R), headaches (R), chest tightness (R), mydriasis (R), abdominal pain (R), and tremor (R) of the hands and feet

iii. **Drug interactions:** can occur with concomitant barbiturate use resulting in excessive sedation

iv. **Contraindications:** none known

E. Ayurvedic Remedies

1. **Common uses:** The first aim of Ayurveda is to reduce the occurrence of disease through breathing exercises, yoga, and herbal intervention.
2. **Adverse effects:** The breathing exercises and yoga are unlikely to cause serious harm if done under proper supervision. Some ayurvedic medications have been adulterated with heavy metals and even corticosteroids. Those that contain arsenic or mercury can produce typical skin lesions and arsenical neuropathy (R).
3. **Drug interactions:** depends on the herbal preparation used; as many of the herbs listed above are used in Ayurveda.

F. Homeopathy

1. Nasal Ease™, used in allergy relief; contains hydroxymethylcellulose as a carrier for various homeopathic remedies with a decrease in allergen diffusion and increase in therapeutic retention on nasal mucosal surface.
2. In general, many homeopathic preparations contain highly diluted metals that theoretically could cause heavy metal systemic toxicity when used in the highest (least therapeutic concentration) (U).

G. Aromatherapy

1. **Common uses:** Aromatherapy is used to reduce anxiety and stress, promote healing and reduce pain.
2. **Adverse effects:** Phototoxic dermatitis from 5-methoxypsoralen; photo-contact dermatitis, immediate contact reactions, and pigmentary changes (R); cutaneous reactions to fragrances (C) affects approximately 1% of the general population with axillary dermatitis, dermatitis of the face (including the eyelids) and neck, well-circumscribed patches in areas of "dabbing-on" perfumes (wrists, behind the ears), and exacerbation of hand eczema. Frequent use of lavender oil can cause a contact dermatitis (C).
3. **Drug interactions:** Eucalyptus oil can decrease blood levels of pento-barbital and amphetamines.
4. **Contraindications:** theoretically can cause bronchoconstriction (R). Oils should never be taken by mouth, and one must avoid any open flames while using aromatherapy.

H. Moxibustion

1. **Common use:** chronic fatigue, malaise, depression, ulcerative colitis, parasitic infection, and breach birth
2. **Adverse effects:** third-degree burns that are directly related to burning the various materials (C)
3. **Drug interactions:** none
4. **Contraindications:** none

I. Acupuncture

1. **Common uses:** chemotherapy-induced nausea, back pain, osteoarthri-tis, addiction, asthma, bronchitis, fibromyalgia, headaches, Irritable bowel syndrome (IBS), and menstrual pain
2. **Adverse effects:** Acupuncture needles can reach vulnerable structures and cause adverse effects such as pneumothorax (R), cardiac tamponade (R), direct injury to nerve roots and spinal cord (R), as well as infectious complications such as hepatitis, staphylococcal septicemia, bacterial endocarditis, and HIV infection. Contact dermatitis can occur from the nickel-based acupuncture needles (C).
3. **Contraindications** include an unstable spine, severe clotting disorder, valvular heart disease, neutropenia, and lymphedema (R).

J. Vitamins and Minerals

1. These agents are unlikely to cause allergic or pseudoallergic reactions although vitamin K and iron dextran can cause anaphylactoid reactions (R) upon rapid infusion, and chondroitin and dextran infusions can cause serum sickness reactions (R).
2. Dietary supplements used in CAM interventions at times can restrict intake of specific nutrients resulting in cases of nutritional rickets (lack of vitamin D) and protein deficiency

("kwashiorkor").

3. Vitamin E reduces oxidative damage *in vivo* and is associated with lower IgE levels and lower frequency of allergen sensitization. Vitamin E was no better than placebo in allergic rhinitis symptom severity scores and serum IgE levels. Gamma-tocopherol, a specific component of vitamin E, blocks enhancement by ozone in an allergen-induced asthma model, attenuating both ovalbumin or ozone-stimulated eosinophilic infiltration and increases of bronchial alveolar lavage fluid cystinyl leukotrienes, Monocyte chemoattractant protein (MCP-1), IL-6, IL-5 and IL-13 mRNA.

K. Antioxidants

1. The term "oxidative stress" refers to the imbalance between reactive oxygen species, which can be harmful, and antioxidants. Examples of endogenous antioxidants include **superoxide dismutase (SOD), catalase, glutathione peroxidase, and glutathione S-transferase**. Oxidative stress occurs as a result of environmental factors as well as inflammation and plays a role in the development and exacerbation of allergic diseases, including allergic rhinitis.
2. **Nitric oxide** (NO) regulates many molecular and cellular functions. It is produced *in vivo* in part due to the presence of nitric oxide synthase (NOS). NO is present in exhaled air, and concentrations of exhaled NO increase with allergic rhinitis. The NOS inhibitor, L-NAME, is no better than controls for the treatment of allergic rhinitis.[2]
3. **Superoxide dismutase** (SOD) is an antioxidant found in the epithelial-lining fluid and epithelial cells of the airways that protects cells against oxidative stress by converting superoxide radicals to hydrogen peroxide. However, exogenous SOD fails to attenuate allergic nasal congestion symptoms in a canine model of allergic rhinitis.
4. **Rosmarinic acid** use in allergic rhinitis significantly decreases symptom scores, numbers of neutrophils and eosinophils in nasal lavage fluid, and decreases reactive oxygen radical production.
5. **Aller-7/NR-A2** is a polyherbal formulation consisting of seven herbal extracts, which significantly decreases symptoms of allergic rhinitis. Aller-7, like rosmarinic acid, appears to act through anti-inflammatory and antioxidant pathways.
6. **Quercetin** is a flavonoid aglycone of rutin found in many vegetables, fruits, and herbs, which is a medicinal herb with significant antioxidant and anti-inflammatory properties. Quercetin inhibits the inflammatory process through membrane stabilization of activated neutrophils, perhaps by inhibiting hyaluronidase, which prevents the breakdown of collagen matrix proteins. Quercetin can prevent mast cell and basophil degranulation, neutrophil lysosomal enzyme secretion, and leukotriene production. Quercetin inhibits antigen-stimulated histamine release, more than sodium cromoglycate in perennial allergic rhinitis.

III. SKIN TESTING EFFECTS OF HERBALS (ANTIHISTAMINIC POTENTIAL)

A. In general, herbal agents, when taken as a single dose, demonstrate minimal inhibition of skin testing (see Table 22-2). It is unclear whether extensive use would have effects on skin testing results and thus practitioners need to consider this when aberrant results occur when testing with

herbal agents such as licorice and milk thistle (see Table 22-3).

Table 22-2 Herbal Supplements that *Do Not Affect* Skin WhealingResponse

Herbal Supplement	Typical Dosage
Aloe	25 mg
Bilberry	80 mg
Cascara sagrada	500 mg
Cat's claw	500 mg
Cayenne	500 mg
Devil's claw	150 mg
Echinacea	300 mg
Evening primrose	500 mg
Garlic	810 mg
Ginger	500 mg
Ginkgo	50 mg
Ginseng	500 mg
Goldenseal	500 mg
Gotu kola	500 mg
Grape seed extract	50 mg
Valerian	500 mg

Table 22-3 Effects of Commonly Used Herbal Supplements onHistamine Skin Prick Testing

Herbal supplements that decrease skin whealing		
Herbal Supplement	**Daily Dosage**	**% Decrease in Whealing Response**
Licorice	500 mg	−21%
Green tea	150 mg	−19%
Saw palmetto	500 mg	−19%
St. John's wort	300 mg	−15%
Feverfew	500 mg	−15%
Herbal supplements that increase skin whealing		
Herbal Supplement	**Daily Dosage**	**% Increase in Whealing Response**
Milk thistle	200 mg	+24%
Astragalus	250 mg	+15%

(From More DR, Napoli DC, Hagan LL. Herbal supplements and skin testing: the lack of effect of commonly used herbal supplements on histamine skin prick testing. *Allergy* 2003;58(6):492–494, with permission.)

IV. MEDICOLEGAL

A. The medicolegal implications of complementary and alternative therapy are just beginning to be worked out in the legal system, and a complete analysis is beyond the scope of this chapter; however, we provide a basic framework for any practitioner who would incorporate CAM in his or her practice. The most basic tenet of malpractice litigation is determining whether a physician failed in his or her duty to provide a patient the "standard of care" as defined by local/regional practitioners, medical experts, and the medical literature. Any deviation from the "standard of care" that subsequently results in actual injury to the patient can be considered grounds for malpractice. The emergence of CAM therapeutics as a medical discipline is still evolving, and therefore, no "standard of care" has been defined and most prescribers of CAM (both allopathic physicians and more traditional CAM practitioners) live in a legal limbo as to the liability risks of their practice.

B. Most physicians who work with CAM do not provide it in their own office but refer patients out to more experienced practitioners, such as acupuncturists, naturopaths, or chiropractors. Physicians often take for granted our ability to refer patients who actively seek out CAM to reputable practitioners; however, this was not always the case. It took until 1983 and two

lawsuits, requiring the American Medical Association to remove disparaging references to chiropractic practices from the association's position on medical ethics. Until that time, it was considered unethical for a physician to refer any patient for treatment to anyone other than another licensed physician. Many states require CAM practitioners to be licensed and have set up educational requirements to practice. For example, the state of New York requires licensed acupuncturists to undergo 200 classroom hours of anatomy, physiology, and pathology; 600 classroom hours of acupuncture theory, and 650 hours of supervised clinical practice. Naturopathic doctors are licensed mostly in the Western United States, with legislation pending in other states; some states are requiring a passing grade on a state licensing exam. All 50 states require chiropractors to be licensed. Therefore, the liability that exists when a physician refers a patient to a CAM practitioner may be mitigated by the state's legitimizing CAM therapies through this credentialing process. By creating a licensing board (and in some cases, exams), states are helping to define the "standard of care" for CAM, which has resulted to some insurance companies adding coverage of CAM in some of their products. **C.** The liability risks are higher for those physicians who provide CAM therapy in their office (i.e., integrative medicine practices). Any physician who chooses to offer CAM therapies in her or his practice should seek counsel from a lawyer specializing in CAM therapies as different states have different regulations. Equally important, physicians should discuss any potential usage of CAM with their malpractice provider to ensure adequate coverage in case of poor outcome.

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23

Building-related Illness

Jessica Savage and Robert A. Wood

I. INTRODUCTION

The chapter focuses on illnesses associated with indoor exposures. The term building-related illness (BRI) originated after health complaints associated with indoor working environments—primarily office buildings—became prevalent in the 1970s and the 1980s. The term was developed to contrast with "sick building syndrome (SBS)" (see below) in which nonspecific complaints are prevalent and a clear pathophysiologic basis has not been identified. Other sections of this book focus on the specific allergens present in indoor environments and the more typical allergic symptoms they cause. While some BRIs are related to specific allergen exposures, other factors that may be more difficult to ascertain are also thought to play a significant role in BRI.

The chapter highlights nonoccupational exposures and includes residential and office environments. Patients with suspected building-related complaints may seek the advice of a primary care doctor, allergist/immunologist, toxicologist, or occupational health clinic. Therefore, the chapter draws from the literature from those specialties. However, we highlight exposures and diagnoses of interest to the practicing allergist/immunologist.

In addition to typical allergens like dust mites or animal danders, there are multiple additional features of the indoor environment relevant to human disease. The one that has garnered the most attention in the press is the presence of fungi or mold, particularly related to damp indoor spaces. However, there are other features of the indoor environment of potential significance, especially including the presence of other allergens and irritants such as volatile organic compounds (VOCs). The exact role of all of these components in BRI has not been fully elucidated.

The following mechanisms of BRI have been described: immune, infection, intoxication (mycotoxicity), and irritation (Table 23-1). In addition to discussing specific BRI, we review practical issues related to BRI including related syndromes, key components of the medical history and physical examination, and the interpretation of reports of environmental assessments.

Table 23-1 Mechanisms of Building-Related Illness

- Immune
- Infection
- Intoxication (mycotoxicity)
- Irritation

A. Sick Building Syndrome/Irritant Syndromes

The term sick building syndrome (SBS) was introduced in the 1970s after a high prevalence of complaints was reported in workers in newer office buildings that did not have natural ventilation. Over the years, several definitions for SBS have been used. Further, some of the features of what was originally referred to as SBS have been determined to have a pathophysiologic basis and are now considered BRIs.

Today, SBS generally refers to medical symptoms with an unclear cause that have a possible relation to the indoor environment. According to the Environmental Protection Agency's (EPA) definition, SBS occurs when building occupants complain of symptoms associated with acute discomfort, for example, headache; eye, nose, or throat irritation; dry cough; dry or itchy skin; dizziness and nausea; difficulty in concentrating; fatigue; and sensitivity to odors. Most of the complainants report relief soon after leaving the building. The cause of SBS is unknown (Table 23-2).

Table 23-2 EPA Definition of Sick Building Syndrome

- Building occupants complain of symptoms associated with acute discomfort, for example, headache; eye, nose, or throat irritation; dry cough; dry or itchy skin; dizziness and nausea; difficulty in concentrating; fatigue; and sensitivity to odors.
- The cause of the symptoms is not known.
- Most of the complainants report relief soon after leaving the building.

(www.epa.gov, accessed March 15, 2011)

Depending on the definition used, symptoms can include neurobehavioral symptoms (e.g., memory loss, headache, depression, dizziness) and complaints involving the eyes (irritation, pain, redness), skin (rashes, dryness, pruritus), and upper airways (congestion and rhinorrhea). The pathophysiologic mechanisms explaining how environmental factors cause SBS remain elusive, although SBS has been associated with lower ventilation rates.

B. Multiple Chemical Sensitivity

Multiple chemical sensitivity (MCS), or idiopathic environmental intolerance (IEI), is an acquired chronic disorder characterized by multiple recurrent symptoms that affect different organ systems. Patients consider it to be caused by exposure to low levels of environmental chemicals, which are at a well-tolerated concentration for the majority of the population. The definition of MCS can vary between authors, and the cause of MCS–IEI is unclear. The study of Dalton and Jaén (2010) suggests that MCS patients have differences in cognitive processing of odors rather than differences in sensitivity or susceptibility to chemicals.

II. PATIENT EVALUATION

Like with all patient encounters, a comprehensive medical history and thorough physical exam should be undertaken.

A possible link between exposure and symptoms may be established on the basis of observation and correlation.

A. History. It is advisable to search for a change in the environment related to symptom onset or exacerbation, rather than seeking information on specific exposures. It is important to elicit specific symptoms as well as the timing of those symptoms in relation to presence in the home or work environment (Table 23-3). Did the symptoms begin after starting a specific job or moving into a new location? Do the symptoms abate over the weekend or while on vacation? Do they progress throughout the day? Are they worse at home or at work? Do they come on immediately, or gradually? Do they resolve with leaving the building, or over a longer period of time? Are other individuals in the building experiencing similar symptoms? The history should also include some information about the work organization and factors such as job satisfaction, level of

stress, and relationships with coworkers and supervisors.

Table 23-3 Helpful Questions in Taking the Medical History

1. Did the symptoms begin after starting a specific job or moving into a new location?
2. Do the symptoms abate over the weekend or while on vacation?
3. Do they progress throughout the day?
4. Are they worse at home or at work?
5. Do they come on immediately, or gradually?
6. Are other individuals in the building experiencing similar symptoms?

B. Examination. A thorough physical examination should be performed. Patients with building-related symptoms may have important physical findings, such as conjunctival injection, turbinate edema, urticaria, eczema, or an abnormal pulmonary exam. Further, patients with rheumatologic or other multisystem disease may initially attribute their symptoms to the indoor environment and present to an allergy/immunology clinic.

C. Assessment of Home/Work Environment. It is important to elicit specific characteristics of the home and work environment (Table 23-4). What is the patient's job? Are there specific chemical or allergen exposures at work? Is there a damp area? Has the area been flooded? Is there visible mold? What is the heating/cooling system? What structures are nearby? Has any building inspection been done for mold/bacteria? Have there been any recent changes to the home or work environment?

Table 23-4 Helpful Questions in Taking the Home/Work Environment History

1. What is the patient's job?
2. Are there specific chemical or allergen exposures at work?
3. Is there a damp area?
4. Has the area been flooded?
5. Is there visible mold?
6. What is the heating/cooling system?
7. What structures are nearby?
8. Has any building inspection been done for mold/bacteria?
9. Have there been any recent changes to the home or work environment?

D. Laboratory Evaluation. Additional investigations including laboratory and radiologic may be relevant depending on the history and physical examination findings and the differential diagnosis in question. Assessment for IgE antibodies to mold antigens has clearly been validated as a measure of potential allergic reactivity to mold. However, as with all allergy testing, a positive skin test or specific IgE antibody to molds or other allergens without appropriate clinical evaluation should not be taken as an indicator of clinical disease. In addition, the presence of IgE antibodies to an allergen cannot be used to determine the dose or timing of prior exposures.

Measurement of IgG antibodies has clinical relevance in the evaluation BRI such as of hypersensitivity pneumonitis (HP). While immunoprecipi-tation measures all classes of antibodies present, it primarily detects IgG antibody. Such testing is appropriate to perform only in the setting of a clinical picture including history, physical exam, imaging, and other laboratory studies suggesting HP as part of the differential diagnosis. Unfortunately, the test is not sensitive, and as many as half of highly exposed individuals might have precipitating antibodies in the absence of clinical disease. Testing for antibodies for mycotoxins has not been validated.

E. Additional Issues. Physicians investigating BRI must demonstrate concern for the occupants of

the building, the employer (in the case of office building related issues), and the owner of the building. Failing to do so may contribute to iatrogenic illness with uncalled-for disability, unemployment, and litigation and/or inappropriate renovation of buildings.

III. CLINICAL SYNDROMES OF BRI

A. Asthma. Allergens, irritants/chemicals, and potentially overall dampness constitute significant precipitating factors for asthma in indoor environments. Asthma exacerbations have been associated with many indoor allergen exposures including dust mites, animal danders (e.g., cat, dog), pests (e.g., cockroach, mice), and mold in sensitized individuals. Salo et al. (2008) also demonstrate that concentrations of several allergens including dust mite, dog, Alternaria, cat, cockroach, and mouse in the indoor environment are associated with asthma incidence. Upper and lower respiratory tract infections caused by exposure to viruses and bacteria are also major precipitants of acute asthma exacerbations, and there is evidence that building characteristics such as occupant density and ventilation rate are associated with the prevalence of respiratory illness.

Indoor air contaminants that may exacerbate asthma include cigarette smoke (both active and passive) and nitrogen dioxide, especially from gas appliances in poorly ventilated spaces. Further, there is suggestive evidence that fragrances, as well as VOCs (see below), especially formaldehyde, can cause or exacerbate lower respiratory symptoms. Outdoor pollutants may also contribute to indoor air quality and cause asthma symptoms, including ozone, particulate matter, and sulfur dioxide. The role of these irritants as well as the effects of ventilation rate on BRI is under active research.

B. Allergic Rhinitis and Conjunctivitis. Upper airway complaints include nasal itching, nasal congestion, rhinorrhea, and sneezing. Other symptoms may include sinus headaches, scratchy throat, and hoarseness. Conjunctival involvement may include itching, watering, redness, and puffy eyes. Physical findings at the time of patient evaluation may be normal. The triggers and pathophysiology of allergic rhinitis and conjunctivitis are similar to what is identified in the lower airways, including allergic and nonallergic stimuli, although the role of chemical irritants has been less well demonstrated.

C. Cutaneous Manifestations. Contact dermatitis may occur after chemical exposures, including cleaning products. Exposure to chemical and irritant particulates (e.g., from insulation materials) can cause a rash on exposed areas of skin. In sensitized subjects, urticaria and eczema may occur after exposure to allergens in the indoor environment. Dry and itchy skin is associated with the use of mechanical ventilation in office buildings although the mechanism is unknown.

D. Hypersensitivity Pneumonitis and Humidifier Fever. HP is a complex allergic disease that results from inhalation of organic dust (see chapter on Immunologic Lung Disease for a more complete discussion). HP is primarily an occupational disease, and the dust may be of bacterial, fungal, vegetable, or avian origin. High dose and/or prolonged exposure is thought to be necessary for sensitization and disease manifestation. Rare cases have been reported from chemical exposures, both occupationally and in the health care setting (i.e., medications).

The clinical manifestations of HP are acute episodes of pneumonitis associated with the particular sensitizing exposure. Specific diagnosis is performed by testing for IgG antibody to allergen and testing for the presence of precipitins in the Ouchterlony double diffusion assay.

Humidifier fever is a variant of HP resulting from inhalation of bacterial and fungal allergen that has been aerosolized via the humidifier. Typically, the symptoms are of shorter duration and include fever. It has been reported in the occupational and residential setting and suspected in the recreational setting (hot tub users).

E. Infections. Unfortunately, several bacterial infections have caused outbreaks associated with indoor exposures. These include the well-known *Legionella pneumophila* outbreak in a Philadelphia hotel in 1976, which was ultimately determined to be from colonization in the hotel's ventilation system. In the case of mold, the American College of Occupational and Environmental Medicine advises that individuals who are immunocompro-mised avoid areas of uncontrolled mold growth as well as areas where bird droppings may contaminate the source of air intake. Other serious infectious diseases can be spread indoors. However, most of these are unlikely to be initially seen by an allergist/immunologist, and therefore, the topic of infection is mentioned only for completeness.

Of interest to the allergist, however, is the well-known fact that viral infection can trigger lower respiratory symptoms both in patients with preexisting asthma and those without a known diagnosis of asthma or atopic disease. The indoor environment has been associated with increased lower respiratory illness and respiratory infection. For example, Zuraimi et al. (2007) present data indicating an association between air-conditioning and a higher prevalence of lower respiratory illness and rhinitis in children. Fisk et al. (2010) demonstrated that residential dampness and mold presence are associated with substantial increases in respiratory infections and bronchitis using meta-analysis. The mechanism underlying these associations is unknown.

F. Mycotoxicity. Both bacteria and fungi can produce toxins that cause human disease. Exposure to these toxins occurs by inhalation, dermal contact, and ingestion. In the indoor environment, ingestion is unlikely to be a factor and is not considered in this chapter. In this section, our discussion focuses upon fungal-derived toxins, or mycotoxins.

Studies on the human effects of fungal-derived toxins are limited. This is in part due to the difficulties defining intricacies of the pathway from source to aerosolization and exposure, to tissue deposition and potential tissue damage. In experimental animals and cell lines, studies have shown adverse effects including immunotoxic, neurologic, respiratory, and dermal responses after specific toxin exposures. Several mycotoxins have been shown or suspected to be carcinogenic in humans when ingested. However, the human carcinogenic data that have implicated inhalation as a route of exposure were related to massive exposures to grain or peanut dust that contained spores with aflatoxin at concentrations many times higher than those thought to be present in indoor, nonagricultural environments.

In the case of mold toxins, the dose of inhaled toxin required to cause adverse effects in humans has not been determined, and it is generally assumed that only a limited dose could be received by persons from a building-related exposure. It has been demonstrated that trichothecene mycotoxins can be aerosolized and be inhaled. Further, toxins have been detected in blood and urine of persons exposed via inhalation. However, the relevance of this observation to human disease has not been defined. Evidence of dermal toxicity has also been suggested. Trichothecenes, a class of mycotoxin produced by several fungi, have been shown to cause an ery-thematous, edematous skin lesion in case reports from exposed construction workers, as well as in animal models, but are unlikely to play a role in typical indoor environments. Currently, there is no substantive evidence to imply that inhaling

mycotoxins or mold in an indoor environment is responsible for any serious health effects other than allergies/hypersensitivity disorders or transient irritation in immunocompetent individuals.

The fungus *Stachybotrys chartarum* received a great deal of attention in the popular media and is therefore worth mentioning in this review. It is commonly found in water-damaged buildings although has been reported as normal flora in non–water-damaged buildings as well. It can produce trichothecene mycotoxins and was given the name "toxic black mold." While elevated levels of *Stachybotrys* can cause severe illness in experimental animals, illness in humans at levels commonly encountered has not been demonstrated. *Stachybotrys* was initially associated with an outbreak of idiopathic pulmonary hemorrhage; however, the CDC later retracted their initial report.

G. Irritant-induced Clinical Symptoms. Aside from environmental tobacco smoke, the evidence that specific irritants in the indoor environment cause BRI remains controversial. However, many building-related complaints appear to be related to nonspecific irritation of the mucus membranes that are assumed to be due to irritants in the environment. While the specific irritants have often not been definitively established, there is greatest evidence that VOCs, as well as particulates, lead to adverse reactions in indoor environments. VOCs are organic molecules that exist as free vapors or are adsorbed onto particles in air. They are used in building materials and are also produced by residential fungi and bacteria. Particles such as fungal structural components are not volatile, and their clinical relevance in a non-occupational setting is unclear.

While VOCs, and in particular formaldehyde, are often implicated in subjective irritant syndromes, the mechanism by which this occurs is not clear. Further, studies are mixed in that higher VOC levels are not always associated with increased irritant symptoms. One study demonstrated that 3-methylfu-ran, a fungal VOC, increased blinking frequency and nasal lavage myeloper-oxidase and lysozyme in acute challenge tests, despite the absence of subjective complaints by volunteers. Other mechanisms by which VOCs may cause irritant effects include stimulation of histamine release as well as induction of oxi-dative stress. The clinical significance of these potential pathways is unknown.

Physical factors may also cause mucus membrane irritation. For example, low humidity may cause irritable discomfort in the eyes, nose, and skin. Working at computers may alter blinking frequency, leading to ocular irritation. Eye, skin, nose or throat, and lower respiratory symptoms are associated with air-conditioned buildings compared to naturally ventilated buildings, although the mechanism is unclear. Elevated temperature may cause mucosal irritation, headache, and fatigue.

H. Other Effects. Concerns about neurotoxicity, immune dysregulation, and rheumatologic illness have been raised related particularly to the role of molds in BRI. The human evidence for an association between mold exposure and these classes of illness has largely been based on case series and case–control studies of questionable validity. We agree with the Institute of Medicine report that found that there was inadequate evidence to determine if there is an association between exposure to damp indoor environments (as a surrogate for mold exposure) and these illnesses. Table 23-5 summarizes the findings of the Institute of Medicine's report on the association between exposure to damp environments and human health effects.

Table 23-5 Summary of Findings of the Institute of Medicine Regarding the Association between Health Outcomes and Exposure to Damp Indoor Environments

Sufficient evidence of a causal relationship
- No outcomes meet this definition

Sufficient evidence of an association
- Upper respiratory symptoms
- Cough
- Wheeze
- Asthma symptoms in sensitized persons with asthma

Limited or suggestive evidence of an association
- Dyspnea
- Lower respiratory illness in otherwise healthy children
- Asthma development

Inadequate or insufficient evidence to determine whether an association exists
- Airflow obstruction in otherwise healthy persons
- Mucus membrane irritation syndrome
- Chronic obstructive pulmonary disease
- Inhalation fevers (nonoccupational)
- Lower respiratory illness in otherwise healthy adults
- Acute idiopathic pulmonary hemorrhage in infants
- Skin symptoms
- Gastrointestinal symptoms
- Fatigue
- Neuropsychiatric symptoms
- Cancer
- Reproductive Effects
- Rheumatologic and other immune diseases

IV. INTERPRETATION OF BUILDING INSPECTION REPORTS WITH MOLD COUNTS

Guidelines for performing and interpreting building inspections can be found in the literature, especially the guide by Horner et al. (2008) for mold inspections. Unfortunately, there are no standardized protocols for sampling the indoor environment in relation to mold presence, and therefore, interpretation of results from building inspections can be challenging. Because most indoor mold is primarily from outdoor sources, it is imperative that samples be taken from the outdoor environment (typically multiple samples) at the same time as indoor sampling. Tw o main sampling techniques include “grab” airborne samples and “source” samples (surface or settled dust). The analysis of samples can be done in several ways; each way has its own advantages and disadvantages. For example, microscopy provides total spore levels and is relatively easy but does not provide any estimate of viability. Laboratory culture allows for species identification, but only for those fungi that are culturable, and only provides information on viable fungi. Other methods based on antigen detection and DNA presence have been developed, although the clinical relevance of these assays has not been fully demonstrated. Some authors advocate for personal monitoring rather than area sampling; however, this is not done routinely.

As there are no accepted standards for indoor fungi exposure, interpretation is guided by patterns rather than specific quantities. Differences between indoor and outdoor results suggest but do not confirm that mold growth is present indoors. Caution is needed to not overinterpret such an observation, or to consider that observation definitive, as variability in season may cause increased levels of fungi indoors or there may have been recent disturbance of indoor dust. The presence of fungal reproductive structures suggests fungal growth on surfaces, whereas the presence of miscellaneous spores on surfaces does not necessarily indicate indoor fungal growth.

V. PREVENTION AND REMEDIATION

Prevention strategies have been suggested for SBS and may be applicable to BRI. They include maintaining an outdoor air supply of more than 10 L per second per person; selecting building materials, furnishings, and equipment that are least likely to release pollutants such as formaldehyde or VOC; ensuring proper maintenance and cleaning; and avoiding materials that may act as substrates for the proliferation of microbes or dust mites. In the specific case of damp environments and mold exposure, the Institute of Medicine Damp Indoor Spaces and Health volume provides an excellent review.

A. Economic Impact

As outlined above, there are gaps in our collective knowledge on the mechanism of BRI. However, the significance of BRI is highlighted when one considers it to be a disease associated with an exposure and therefore potentially preventable. In a 2002 analysis, Mendell et al. estimated that potential annual reductions in adverse health effects include 5 to 7 million communicable respiratory infections, a 6% to 15% reduction in exacerbations in asthma, and a 20% to 50% reduction in nonspecific building-related symptoms, if improvements are made to indoor environments. They estimate that the combined annual cost of the adverse health effects range from $50 to $100 billion, with about $5 to $75 billion potentially preventable. While some of these costs may be related to SBS rather than BRI, the economic impact of BRI is clearly significant.

VI. SUMMARY AND CONCLUSIONS

BRI refers to illness associated with indoor exposures, for which a patho-physiologic basis has been identified. The most validated forms of BRI of importance to the allergist include hypersensitivity disorders such as asthma as well as H P. In addition, by bringing people into close contact, buildings can be a source of infection. The role of toxin-mediated and irritant-related disease in BRI is less clear. Treatment of BRI will be guided by the underlying disease identified.

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Appendix I

Skin Testing Methods

Nkiruka U. Erekosima and Sarbjit S. Saini

The methods described in this appendix were adapted from the updated **Practice Parameter on Allergy Diagnostic Testing** established by the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI).

I. PERCUTANEOUS (ALSO KNOWN AS PRICK OR PUNCTURE) SKIN TESTING

Clean the skin area to be tested with alcohol and allow it to dry. Mark and label the test sites on the volar surface of the forearm or on the upper back at least 2 to 2.5 cm apart to avoid any overlapping of positive skin reactions. Skin tests should not be placed in areas 5 cm from the wrist or 3 cm from the antecubital fossae. Using the prick technique, a sharp device (hypodermic needle, solid-bore needle, blood lancet) is passed through a drop of extract or control solutions (histamine, saline) at a 45- to 60-degree angle to the skin. The skin is then gently lifted, creating a small break in the epidermis through which the allergen solution penetrates. Alternatively, the puncture technique can be utilized. With this technique, the device is introduced through the drop at a 90-degree angle to the skin. Devices used in this manner generally are designed to prevent excess penetration into the dermis. The skin should not be punctured so deep as to cause bleeding. Devices with multiple tips have also been developed to apply several skin tests at the same time. Of note, lancet instruments, either coated or submerged in a well containing the allergen extract (Phazet, Prilotest), are not used in the United States.

It was previously a common practice to use a single metal bifurcated needle to test multiple allergens on the same patient. In this method, the device tip is wiped clean with alcohol between tests. According to the Occupational Safety and Health Administration, this technique could potentially expose the technician to unintentional pricks and blood-borne pathogens. Hence, many allergists have abandoned the use of solid-bore needles for percutaneous testing and choose to use the newer devices, each of which is discarded after single use. Of note, studies comparing the reliability and variability of various skin test devices have demonstrated significant differences among them in terms of the wheal size that they produce, using either saline or histamine. It is, therefore, imperative to adhere consistently to the criteria for negative and positive reactions when interpreting results with any of these products. In choosing a skin test device, the practitioner can consider several factors including reliability, safety, cost, convenience, and patient comfort. Positive and negative controls should be performed with all tests. For many years in the United States, the only available positive control was histamine phosphate (2.7 mg/mL equivalent to a 1.0-mg/mL histamine base), producing wheal diameters ranging from 2 to 7 mm. Another positive control, a 10-mg/mL histamine dihydrochloride control, currently is available, and this is the preferred positive control for prick/puncture skin tests. The negative control

consists of 50% glycerinated human serum albumin (HSA)–saline if concentrated extracts are used.

Reading and Interpreting the Test Results

Fifteen to twenty minutes after administering the allergen prick/puncture skin test (i.e., the peak reactivity time), **measure the longest and orthogonal diameters of any resultant wheal and record the average of the two.** Do the same procedure for any resultant erythema. Also measure values for positive and negative controls and record all values in millimiters. Marking the boundaries of these skin changes with a pen can facilitate their evaluation. Note any **pseudopod** formation because this denotes a significantly positive reaction. An average wheal diameter of at least 3 mm (with equivalent erythema) greater than the diluent control done at the same time is considered to be positive. Qualitative scoring (such as 0 to 4; positive or negative) is no longer used by many clinicians because of interphysician variability in this method of scoring and interpretation. Since trauma may affect wheal size, an allergen response smaller than 3 mm generally should not be regarded as positive. Devices that produce wheals that exceed 3 mm at negative control sites should be avoided.

II. INTRACUTANEOUS (ALSO KNOWN AS INTRADERMAL) SKIN TESTING

Intracutaneous skin testing could be considered only after a negative percutaneous test result is obtained despite a history strongly suggestive of allergen sensitivity and of relevant exposure. In addition, intracutaneous skin testing can be used to evaluate skin sensitivity to low-potency allergenic extracts. **This method is also preferable for diagnosis of drug and venom anaphylaxis. This method, however, should not be used in the evaluation of possible food sensitivity to avoid either false-positive results in nonallergic individuals or systemic reactions in highly allergic individuals.**

The updated Practice Parameter on Allergy Diagnostic Testing cites that intracutaneous tests are usually placed on the upper arm or volar surface of the forearm rather than the back in order to allow for application of a tourniquet should systemic symptoms occur. In patients with a preceding negative prick/ puncture test result, the starting dose of allergen extract concentration used in this method is typically between 1/1,000 and 1/100 of that used for percutaneous skin testing. For standardized allergens, such as ragweed, grass, dust mite, and cat, the recommended range of starting intracutaneous test solutions in patients with preceding negative prick/puncture test results is between 10 and 100 BAU. The negative and positive controls consist of the diluent solution and histamine, respectively. Clean and mark the skin test area as previously described. Using a single-unit, 0.5- or 1.0-mL disposable syringe with an attached hypodermic needle (needle gauge may vary from 26 to 30), draw approximately 0.02 to 0.05 mL of test solution and expel any air bubble if present. Stretch the skin taut and introduce the needle into the skin at a 45-degree angle with the bevel facing upward. Advance the needle until its bevel is completely under the skin. Inject approximately 0.02 to 0.05 mL of the solution, creating a 1- to 3-mm bleb in the process. If no such bleb is formed, due to a delivery that is either too deep or too superficial as to cause leakage, repeat the procedure at another site.

Reading and Interpreting the Test Results

Intracutaneous tests are read **10 to 15 minutes after injection,** using a similar method as described for prick/puncture tests. Both wheal and erythema diameters should be measured and recorded in millimeters. Any reaction larger than the negative control may indicate the presence of specific IgE antibody. However, because of its greater sensitivity and poor reproducibility, small positive reactions may not be clinically significant. There are no evidence-based studies on standardized intracutaneous test grading. A survey indicates that 85% of board-certified allergists surveyed reported that they used the criterion of 3 mm above the negative control as a threshold for a positive intracutaneous test result.

SELECTED READINGS

Bernstein IL, Li JT, Bernstein DI, et al. Allergy diagnostic testing: an updated practice parameter. *Ann Allergy Asthma Immunol* 2008;100:S1–S148.

Appendix II

Levels of Immunoglobulins in Sera of Normal Subjects by Age

Thomas A. Fleisher

Table II-1 Levels of IgG, IgA, IgM in Sera of Normal Subjects by Age (mg/dL)

Age	IgG	IgA	IgM
0 to <5 mo	100–334	7–37	26–122
5 to <9 mo	164–588	16–50	32–132
9 to <15 mo	246–904	27–66	40–143
15 to <24 mo	313–1170	36–79	46–152
2 to <4 y	295–1156	27–246	37–184
4 to <7 y	386–1470	29–256	37–224
7 to <10 y	462–1682	34–274	38–251
10 to <13 y	503–1719	42–295	41–255
13 to <16 y	509–1580	52–319	45–244
16 to <18 y	487–1327	60–337	49–201
≥18 y	767–1590	61–356	37–286

Values generated by Mayo Medical Laboratories.

Appendix III

Levels of Immunoglobulin E (IgE) in Sera of Normal Subjects by Age

Thomas A. Fleisher

Table III-1 Levels of IgE in Sera of Normal Subjects by Age (kU/L)

Age	Mean	+1SD	+2SD
0–6 wk	0.6	2.3	8.8
7 wk to 3 mo	1.0	4.1	17.0
4–6 mo	1.8	7.3	30.0
7–9 mo	2.6	10.0	39.0
10–23 mo	3.2	13.0	53.0
2 y	5.7	23.0	93.0
3 y	8.0	32.0	128.0
4 y	10.0	40.0	160.0
5 y	12.0	48.0	192.0
6 y	14.0	56.0	224.0
7 y	16.0	63.0	248.0
8 y	18.0	71.0	280.0
9 y	20.0	78.0	304.0
10 y	22.0	85.0	328.0
Adults	13.2	41.0	127.0

Values generated by Mayo Medical Laboratories.

Serum levels of IgE greater than +1SD for age would be consistent with the presence of allergic disease.

Appendix IV

Important Pollen and Fungal Spores in North America

Estelle Levetin, William Neaville, Robert Ausdenmoore, and Robert K. Bush

Table IV-1 Floristic Zones and Allergenic Plants

Zone	Trees/shrubs	Grasses[a]	Weeds
Northern Forest	Coniferous: juniper (*Juniperus, Thuja*), cedar (*Cedrus*), pine (*Pinus*), fir (*Abies*); hardwoods: birch (*Betula*), alder (*Alnus*), aspen (*Populus*), willow (*Salix*), maple (*Acer*)	Pasture grasses (low levels)	Mugwort (*Artemisia*), nettle (*Urtica*), chenopods (*Chenopodium, Kochia*), pigweeds (*Amaranthus*) (all low levels)
Eastern Agricultural	Red cedar (*Juniperus*), pines, white and red oaks (*Quercus*), beech (*Fagus*), elms (*Ulmus*), ash (*Fraxinus*), sycamore (*Plantanus*), maples, box elder (*Acer*), alder, red birch, hickory (*Carya*), black walnut (*Juglans*), locust (*Robinia*), hawthorn (*Crategus*)	Pasture grasses in northeast; ryegrass (*Lolium*), orchard (*Dactylis*), fescue (*Festuca*), brome and chess (*Bromus*), timothy (*Phleum*), sweet vernal (*Anthoxanthum*); southern states: Bermuda (*Cynodon*), Johnson (*Sorghum*)	Short, giant, southern, and western ragweed (*Ambrosia*), mugwort, pigweeds, lamb's quarter (*Chenopodium*), nettle, dock and sorrel (*Rumex*), plantain (*Plantago*)
Central Plains	As in Eastern Agricultural; cottonwood (*Populus*) willow, box elder, locust	As in Eastern Agricultural	As in Eastern Agricultural; Chenopods (*Kochia, Salsola, Atriplex*), pigweeds, waterhemp (*Ancida*)
Rocky	Mountain cedar	Pasture grasses:	Tumbleweeds

Mountain	(*Juniperus*), ponderosa, lodgepole pine (*Pinus*), aspen, willow, box elder, cottonwood, gambel oak, maple, ash	ryegrass, orchard, fescue, brome and chess, timothy	(*Kochia, Salsola*), other chenopods and amaranths, dock (*Rumex*), giant, western ragweed, sagebrush, prairie sage (*Artemisia*)
Northwest Coastal	Cedar, fir, pine, alder, birch, hazel (*Corylus*)	Timothy, orchard, brome, ryegrass, fescue, sweet vernal, velvet grass (*Holcus*)	Plantain, short ragweed, orach (*Atriplex*), amaranths, chenopods, dock, sorrel
California Lowland	Alder (*Alnus*), olive (*Olea*), walnut (*Juglans*), sycamore (*Plantanus*), willow (*Salix*), elm (*Ulmus*) eucalyptus (*Eucalyptus*)	Pasture grasses, Bermuda (*Cynodon*), Johnson (*Sorghum*), velvet (*Holcus*)	Scales (*Atriplex*), Palmer's amaranth (*Amaranthus*), tumbleweeds (*Kochia, Salsola*), *Baccharis*, nettle (*Urtica*)
Arid Southwest	Mountain cedar (*Juniperus*), ash (*Fraxinus*), mulberry (*Morus*), acacia (*Acacia*), mesquite (*Prosopis*)	Pasture grasses, Bermuda, witchgrass (*Panicum*), grama (*Boutleloua*)	Scales, Palmer's amaranth, tumbleweeds
Great Basin	As in Rocky Mountain and Arid Southwest	Pasture grasses, Bermuda, Johnson, witchgrass	Scales, tumbleweeds, rabbitbrush (*Chrysothamnus*), marshelders (*Iva*)
Southeastern Coastal	As in Eastern Agricultural; bald cypress (*Taxodium*), live oak (*Quercus*), box elder (*Acer*), elm, hackberry (*Celtis*), ash, hornbeams (*Carpinus, Ostryia*), hickory, pecans (*Carya*) sweet	As in Eastern Agricultural; bahia and dallis (*Paspalum*)	As in Eastern Agricultural; *Baccharis*
Subtropical Florida	Pine, bald cypress, live oak, mulberry, eucalyptus, palm (*Phoenix, Cocos*), palmetto (*Sabal*)	Bermuda, Johnson, bahia, dallis	Short ragweed (*Ambrosia*), seamyrtle (*Baccharis*), spiny and redroot pigweeds (*Amaranthus*), goosefoots (*Chenopodium*)

Note: Genus listed with first entry in table.

[a]Inclusive of Alaska.

(Modified from Weber RW. Floristic zones and aeroallergen diversity. *Immunol Allergy Clin North Am* 2003;23:357–369).

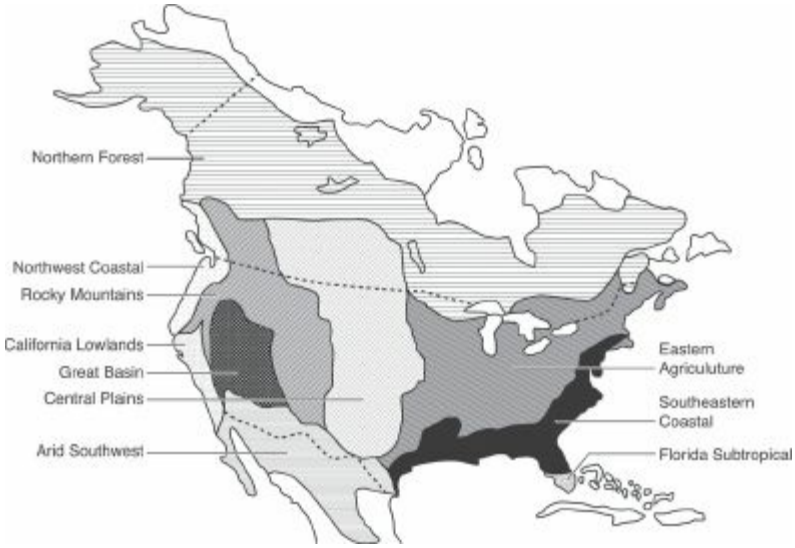

Figure IV-1 Floristic zones of North America. (From Weber RW. Floristic zones and aeroallergen diversity. *Immunol Allergy Clin North Am* 2003;23:357–369, with permission from Elsevier.)

Table IV-2 Commonly Encountered Fungi

Indoor[a]	Outdoor
Penicillium sp.	*Cladosporium (Hormodendron)*
Aspergillus sp.	*Alternaria*
Cladosporium sp. *(Hormodendron)*	*Penicillium*
Alternaria	*Aspergillus*
Geotrichium	*Epicoccum*
Aureobasidium (Pullularia)	*Fusarium*
Yeasts	*Phoma*
Mucor	*Helminthosporium*
Rhizopus	*Drechslera/Bipolaris*
Stachybotrys	*Curvularia*
Chaetomium	*Aureobasidium (Pullularia)*
	Botrytis
	Basidiospores
	Ascospores
	Smut spores
	Myxomycete spores
	Rust spores

[a]Often intrusion from outdoor sources. Species found depends on level of humidity and substrate sources

Appendix V

Educational Resources for Food Allergy

Stephen R. Boden and A. Wesley Burks

The Food Allergy and Anaphylaxis Network
10400 Easton Place, Suite 107
Fairfax, VA 22030-5647
800-929-4040 http://www.foodallergy.org

Kids With Food Allergies, Inc
73 Old Dublin Pike, Suite 10, #163
Doylestown, PA 18901
215-230-5394
http://www.kidswithfoodallergies.org

National Allergy and Asthma Network/Mothers of Asthmatics
2751 Prosperity Ave, Suite 150
Fairfax, VA 22031
800-878-4403
http://www.aanma.org

Asthma and Allergy Foundation of America
1125 15th Street, NW, Suite 502
Washington, DC 20005
800-727-8462
http://www.aafa.org

American Academy Of Allergy Asthma & Immunology
555 E Wells Street, Suite 1100
Milwaukee, WI 53202
414-272-6071
http://www.aaaai.org

Appendix VI

Drug Allergy Procedures

David A. Khan

Table VI-1 Nonirritating Concentrations of Antibiotics Used for Skin Testing

Antimicrobial drug	Nonirritating concentration	Full-strength concentration	Dilution from full strength
Azithromycin	10 µg/mL	100 mg/mL	1:10,000
Cefotaxime	10 mg/mL	100 mg/mL	1:10
Cefuroxime	10 mg/mL	100 mg/mL	1:10
Cefazolin	33 mg/mL	330 mg/mL	1:10
Ceftazidime	10 mg/mL	100 mg/mL	1:10
Ceftriaxone	10 mg/mL	100 mg/mL	1:10
Clindamycin	15 mg/mL	150 mg/mL	1:10
Cotrimoxazole	800mcg/ml	80 mg/ml	1:100
Erythromycin	50 µg/mL	50 mg/mL	1:1,000
Gentamicin	4 mg/mL	40 mg/mL	1:10
Levofloxacin	25 µg/mL	25 mg/mL	1:1,000
Imipenem/cilastin	0.5 mg/mL	500 mg/100 mL	1:10
Meropenem	1 mg/mL	50 mg/mL	1:50
Nafcillin	25 µg/mL	250 mg/mL	1:10,000
Ticarcillin	20 mg/mL	200 mg/mL	1:10
Tobramycin	4 mg/mL	80 mg/2 mL	1:10
Vancomycin	5 µg/mL	50 mg/mL	1:10,000

Table VI-2 Graded Challenge Protocol for History of Immediate Reactions

Likelihood of drug allergy	Example scenario	No. of steps	Starting dose	Dose interval and observation[a]
Unlikely	Remote history of rash to cephalosporin	3	1/100th final dose	30 min between first and second doses with 1 h observation after last dose
Very unlikely	History of penicillin allergy in need of carbapenem	2	1/10th final dose	30 min between doses with 1 h observation after last dose
Extremely unlikely	History of headache after penicillin	1	Full dose	1 h observation

[a]Interval and observation may be modified based on patient-specific factors and clinician judgment

Table VI-3 Classification of Induction of Drug Tolerance Procedures

Mechanism of drug reaction	Duration of procedure	Initial dose	Potential mechanism of drug tolerance	Examples
Immunologic IgE (drug desensitization)	Hours	mcg	Inhibition of internalization of antigen/IgE/FcεRI complex	Penicillin
Immunologic non-IgE	Hours to days	mg	Unknown	Trimethoprim/sulfamethoxazole
Pharmacologic	Hours to days	mg	Metabolic shift, internalization of receptors	Aspirin
Undefined	Days to weeks	mcg-mg	Unknown	Allopurinol

Table VI-4 Oral Penicillin Desensitization (IgE Induction of Drug Tolerance)

Step	PCN V (U/mL)	Dose (mL)	Dose (U)	Cumulative dose
1	**1,000**	0.1	100	100
2	1,000	0.2	200	300
3	1,000	0.4	400	700
4	1,000	0.8	800	1,500
5	1,000	1.6	1,600	3,100
6	1,000	3.2	3,200	6,300
7	1,000	6.4	6,400	12,700
8	**10,000**	1.2	12,000	24,700
9	10,000	2.4	24,000	48,700
10	10,000	4.8	48,000	96,700
11	**80,000**	1.0	80,000	176,000
12	80,000	2.0	160,000	336,700
13	80,000	4.0	320,000	656,700
14	80,000	8.0	640,000	1,296,700

Administer PCN V orally every 15 min per step
Total time: 3 h and 45 min; total dose: 1.3 million U; total volume: 36.1 mL

Preparation of PCN-V solutions

Use penicillin V elixir 250 mg/mL = 80,000 U/mL (1 mg = 1,600 U)
Add 2 mL of 80,000 U/mL PCN to 14 mL normal saline to make 10,000 U/mL PCN V
Add 2 mL of 10,000 U/mL PCN V to 18 mL normal saline to make 1,000 U/mL PCN V

Quantity of PCN-V solutions

No. of syringes	Syringe volume (cc)	PCN-V solution (U/mL)
1	1	1,000
2	10	1,000
1	10	10,000
1	20	80,000

PCN V, penicillin V.

(Modified from Buchmiller BL, Khan DA. Evaluation and management of pediatric drug allergic reactions. *Curr Allergy Asthma Rep* 2007;7:402–409.)

Table VI-5 Intravenous Antibiotic Desensitization (IgE Induction of Drug Tolerance) Protocol

Full dose = 1,000 mg

Preparation of solutions

	Total volume of solution (antibiotic plus diluent, e.g., 0.9% sodium chloride)	**Antibiotic dose** to be injected in each solution bag	**Final concentration of antibiotic solution**
Solution 1	250 mL (25 mL solution 2 + 225 mL normal saline)	10 mg	0.04 mg/mL
Solution 2	250 mL (25 mL solution 3 + 225 mL normal saline)	100 mg	0.4 mg/mL
Solution 3	250 mL	1,000 mg	4 mg/mL

Induction of drug tolerance protocol

Step	Solution	Rate (mL/h)	Time (min)	Administered dose (mg)	Cumulative dose (mg)
1	1	2	15	0.02	0.02
2	1	5	15	0.05	0.07
3	1	10	15	0.1	0.17
4	1	20	15	0.2	0.37
5	2	5	15	0.5	0.87
6	2	10	15	1	1.87
7	2	20	15	2	3.87
8	2	40	15	4	7.87
9	3	10	15	10	17.87
10	3	20	15	20	37.87
11	3	40	15	40	77.87
12	3	75	184.4	922.13	1,000

Total time= 349.4 min

(Modified from Solensky R, Khan DA, Berstein IL, et al. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol* 2010;105:259–273.)

Table VI-6 Allopurinol Induction of Drug Tolerance Procedure

Daily dose	Concentration/ tablet	Amount	Days
50 µg	1 mg/5 mL	0.25 mL	1–3
100 µg	1 mg/5 mL	0.5 mL	4–6
200 µg	1 mg/5 mL	1 mL	7–9
500 µg	1 mg/5 mL	2.5 mL	10–12
1 mg	1 mg/5 mL	5 mL	13–15
5 mg	10 mg/5 mL	2.5 mL	16–18
10 mg	10 mg/5 mL	5 mL	19–21
25 mg	10 mg/5 mL	12.5 mL	22–24
50 mg	100 mg tablet	1/2 tablet	25–27
100 mg	100 mg tablet	1 tablet	28+

Indicated for patients with a history of pruritic, erythematous exanthem following initiation of allopurinol with resolution of rash after discontinuation

Patients who are elderly, have impaired renal function, or have multiple comorbid conditions should use a slower modified protocol with initial daily doses of 10 and 25 µg and up dosing every 5 to 10 days (Modified from Fam AG, Dunne SM, Iazzetta J, et al. Efficacy and safety of desensitization to allopu-rinol following cutaneous reactions. *Arthr Rheum* 2001;44:231–238.)

Table VI-7 Materials and Methods for Penicillin Skin Testing

	Trade name	Manufacturer	Supplied concentration/ dose	Preparation/recon-stitution & dilution for testing
Benzyl-penicilloyl polylysine	PRE-PEN®	ALK-Abello/ AllerQuest	6×10^{-5} M	As supplied
Penicillin G	Pfizerpen®	Pfizer	5,000,000 U	Reconstitute vial with 3.2 mL saline to make 1,000,000 U/mL. Dilute 0.05 mL of 1:1,000,000 U/mL with 4.95 mL saline to make 10,000 U/mL for testing.
Penilloate	Not commercially available	Chemistry laboratory	0.01 M	See: Macy et al. *J Allergy Clin Immunol* 1997; 100:586–591.
Penicilloate	Not commercially available	Chemistry laboratory	0.01 M	See: Macy et al. *J Allergy Clin Immunol* 1997; 100:586–591.

Table VI-8 Aspirin Desensitization (Pharmacologic Induction of Drug Tolerance)

Assessment and premedication (within 1 wk before procedure)
FEV_1 > 70% predicted (optimally)
Start or continue leukotriene modifier therapy.
Start or continue high-dose inhaled corticosteroid and long-acting beta-agonist if poorly controlled asthma.
Systemic steroid burst if low FEV_1 or bronchial instability
If on maintenance systemic steroids, consider doubling daily dose (if on alternate-day steroids, change to daily dose).

Protocol	
Time	Aspirin dose
0	20.25 mg
90 min	40.5 mg
180 min	81 mg
270 min	162.5 mg
360 min	325 mg

Document informed consent and advise the patient it may take several days to complete (most will take 2 days).
FEV_1 and clinical assessment every 90 min and with symptoms
Dosing interval may be extended to 3 h based on individual patient characteristics.
Treat reactions as indicated below.
After the patient is completely stabilized (but not <3 h after the last dose), the provoking dose can be repeated. A persistent >15% decrease in FEV_1, with or without associated symptoms, lasting longer than 3 h despite therapy, is an indication to discontinue the desensitization process for the day.
If nasal, gastrointestinal, or cutaneous reactions occur on day 1, pretreat with H_1 and H_2 receptor antagonists for remainder of procedure.

Medications for treatment of aspirin-induced reactions	
Ocular	Oral or ocular antihistamines
Nasal	Oral antihistamine, topical decongestant
Laryngeal	Racemic epinephrine nebulization and/or intramuscular epinephrine; consider laryngoscopy to exclude vocal cord dysfunction.
Bronchial	Beta-agonists
Urticaria/angioedema	Oral or intravenous antihistamines
Hypotension (exceedingly rare)	Parenteral epinephrine

(Modified from Solensky R, Khan DA, Berstein IL, et al. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol* 2010;105:259–273.)

Table VI-9 LRapid Aspirin Challenge—Desensitization Protocol for Patients with Coronary Artery Disease Requiring Aspirin

Time[a]	Aspirin dose (mg)
0	0.1
15	0.3
30	1
45	3
60	10
75	20
90	40
105	81
120	162
135	325

Primarily indicated for patients with cutaneous reactions to ASA/NSAIDs.

Consider premedication with antihistamine.

[a] May also dose at every 20-minute intervals.

(Modified from Wong JT, Nagy CS, Krinzman SJ, et al. Rapid oral challenge-desensitization for patients with aspirin-related urticaria-angioedema. *J Allergy Clin Immunol* 2000;105:997–1001.)

Table VI-10 Local Anesthetic Skin Testing and Challenge[a]

Skin testing		
Time interval/ observation	**Skin test**	**Dilution**
15 min	Prick-puncture	Undiluted
15 min	Intradermal	1:100
	Subcutaneous challenge	
Time interval/ observation	**Agent**	**Volume**
20 min	Saline (placebo)	1.0 mL
20 min	Local anesthetic	1.0 mL

[a]Subcutaneous challenge protocol not intended for those rare patients with suspected severe IgE-mediated reactions. A lower starting dose (e.g., 0.1 mL, 1:100) with 10-fold dose increases would be more appropriate

Table VI-11 Carboplatin Desensitization (IgE Induction of Drug Tolerance) Protocol

Full dose = 500 mg

Preparation of solutions

	Total volume of solution (carboplatin plus diluent, e.g., 5% dextrose)	**Carboplatin dose** to be injected in each solution bag	**Final concentration of carboplatin solution**
Solution 1	100 mL (10 mL solution 2 + 90 mL 5% dextrose)	5 mg	0.05 mg/mL
Solution 2	100 mL (10 mL solution 3 + 90 mL 5% dextrose)	50 mg	0.5 mg/mL
Solution 3	100 mL	500 mg	5 mg/mL

Induction of drug tolerance protocol

Step	**Solution**	**Rate (mL/h)**	**Time (min)**	**Administered dose (mg)**	**Cumulative dose (mg)**
1	1	2	15	0.025	0.025
2	1	5	15	0.063	0.088
3	1	10	15	0.125	0.213
4	1	20	15	0.25	0.463
5	2	5	15	0.625	1.088
6	2	10	15	1.25	2.338
7	2	20	15	2.5	4.838
8	2	40	15	5	9.838
9	3	10	15	12.5	22.338
10	3	20	15	25	47.338
11	3	40	15	50	97.338
12	3	75	64.4	402.663	500

Total time= 3.8 h

(Modified from Lee C-W, Matulonis UA, Castells MC. Rapid inpatient/outpatient desensitization for chemotherapy hypersensitivity: Standard protocol effective in 57 patients for 255 courses. *Gyn Oncol* 2005;99:393–399.)

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